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WEEKEND SLEEP PHASE DELAY AND THE TREATMENT WITH MELATONIN

By

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A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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Abstract

WEEKEND SLEEP PHASE DELAY AND THE TREATMENT WITH MELATONIN

By

Chien-Ming Yang

Advisor: Professor Arthur J. Spielman

Two studies were conducted to address on the common sleep pattern in young adults to stay up late at nights and to sleep-in in the mornings during the weekends. In Experiment 1 the effects of a simulated delayed weekend sleep pattern and its association with individual circadian type were investigated in 30 subjects. The delayed weekend sleep pattern was shown to decrease the level of sleepiness near bedtime on Sunday night and to impair cognitive and mood functioning on Monday morning. Also, circadian type was shown to have limited capacity in predicting the deficits caused by this delayed weekend sleep pattern. In Experimental 2 the effects of exogenous melatonin in counteracting the impacts of the delayed weekend sleep pattern were explored in 10 subjects. Melatonin administration on Sunday late afternoon was demonstrated to effectively advance endogenous melatonin phase and shorten sleep onset latency on Sunday night, and improve mood status on Monday morning. The acute sedating effect of melatonin administration as a potential adverse effect was also discussed.

Table of Contents

Lists of Tables

Lists of Figures

Page

Experimental 1

Experimental 2

Experimental 1: The effects of a delayed weekend sleep pattern on sleep and functioning

Abstract

The purpose of the present study is: 1) to demonstrate the effects of a delayed sleep schedule during the weekend on Sunday night's sleep and Monday morning's functioning and, 2) to explore the relationship between individual circadian types (e.g. Morningness and Eveningness) and the delayed weekend sleep pattern. Thirty subjects (5 males and 25 females), between the ages of 18 and 31, were recruited from college settings. Five of them were Morning Type, 24 were Neither Type, and only one was Evening Type. A within-subject, counter-balanced design was used in which subjects' sleep schedules at home on two consecutive weeks were manipulated. In one week (baseline condition), subjects followed the same sleep schedule throughout the week. In the other week (delayed-sleep condition), subjects' bedtime and wake-up time on Friday and Saturday nights were delayed by two hours. They were required to call into an automatic time-stamped voice mail system everyday to make sure they were following the designated sleep-wake schedule. Subjects' subjective sleepiness, mood, and sleep were measured on Sunday night and Monday morning with self-rating scales. Also, their cognitive functioning on Monday morning was assessed with a word-list memory test and a word fluency test administered over the telephone. The results showed that subjects' level of subjective sleepiness near bedtime on Sunday evening was decreased following the delayed weekend schedule. Reported subjective sleep on Sunday night showed trends of longer sleep onset latencies and shorter total sleep times in the delayed sleep condition.

On Monday morning, subjects' performance on cognitive tests and subjective mood ratings were significantly impaired by the delayed weekend sleep schedule. However, sleepiness ratings on the SSS showed no difference between the two conditions. With regards to individual circadian types, the data was limited by the insufficient number of Evening Type subjects in our sample. Circadian type yielded a minimal capacity to predict deficits. Other methodological limitations of this field study include potential expectation effects, and the lack of control over the subjects' sleep-wake schedule, daytime behaviors and the manner in which measurements were conducted over the telephone.

Key words: Sleep; Human; Circadian Rhythms; Daytime functioning; Insomnia

Introduction

It is a common practice for young adults to stay up late on weekend nights and to sleep-in on weekend mornings. The delays in bedtime and wake-up time have been shown to be in the range of a half hour to three and a half hours in high school and college students (Allen & Mirabile, 1989; Andrade, Benedito-Silva, Domenice, Arnhold & Menna-Barreto, 1993; Kowalski &Allen, 1995; Lack, 1986; Valdez, Ramirez & Garcia, 1996).

In addition to the decision to stay up late, it has been suggested that the delayed weekend sleep pattern is associated with the tendency of the endogenous rhythm that regulates the daily sleep-wake cycle to drift later in time (Lack, 1986; Valdez et al., 1996). The endogenous rhythm that regulates the timing of the sleep-wake cycle as well as rhythmic changes in various physiological variables is called the circadian rhythm. It is normally synchronized by the 24-hour environmental light-dark cycle. However, when the light-dark information and other time cues are deprived, the intrinsic rhythm of human circadian regulation is approximately 24.2 hours (Campbell, Dawson & Zulley, 1993; Czeisler et al., 1995; Dijk & Czeisler, 1995). Therefore, there is a tendency for circadian rhythms in general, and the sleep-wake rhythm in particular, to drift later in time. The delayed weekend wake-up time may prevent exposure to morning light and allow the drift of endogenous circadian rhythm to occur.

This model also proposes that the mild delay of the endogenous circadian phase on the weekend may result in sleep onset difficulties on weekday nights as well as functional impairment on weekday mornings when shifting back to regular sleep-wake schedule. In high school students, for example, the amount of delay in weekend bedtime has been shown to be negatively correlated with academic performance (Allen, 1992; Kowalski & Allen, 1995) and with the timing of peak alertness on weekday mornings (Allen, 1991; 1992). Furthermore, a subgroup of college students who reported a delayed sleep-wake schedule during the weekend also reported a longer average sleep onset latency (42.7 min) during the weekday and showed poorer school performance compared to other students (Lack, 1986).

However, this previous work consisted of survey and correlational studies. Therefore the results do not imply a causal relationship between the delayed weekend sleep pattern and the reported impairments. Other factors may have contributed to both the sleep pattern and the sleep and performance problems. For example, a student who frequently goes to parties during the weekend would go to sleep late during the weekend and might not perform well at school as well. In fact, weekend party time and alcohol consumption have also been shown to correlate with the amount of sleep delayed during the weekend in high school students (Allen, 1992; Kowalski & Allen, 1995). An experimental study which manipulates the sleep pattern directly is needed to investigate the consequences of delayed weekend sleep pattern.

In addition, a survey of college students reported that the delayed weekend sleep pattern and associated difficulties were only reported in a subgroup of the sample (Lack, 1986). This suggests some individuals are more prone than others to be effected by this sleep pattern.

The Morningness/Eveningness Typology has received a great deal of attention because of its purported relationship to circadian rhythmicity. Categorization depends on the time of day at which an individual is functioning at his/her best measured by a self-rating questionnaire (Horne & Ostberg, 1976). In general, individuals are classified into Evening Type – people who function at best in the evening, Morning Type – people who function best in the morning, and Intermediate Type or Neither Type – people falling in between the two extreme types. Evening Type persons have been shown to have a delayed circadian phase in comparison with Morning Type persons on many behavioral and physiological measures, such as sleep-wake schedule, levels of sleepiness and arousal, cognitive performance, body temperature, salivary cortisol level, and plasma melatonin level (Bailey & Heitkemper, 1991; Breithaupt, et al., 1978; Clodore, Foret & Benoit, 1986; Hall, Duffy, Dijk & Czeisler, 1997; Horne & Ostberg, 1977; Wilson, 1990; for review see Kerkhof, 1985). Therefore, we hypothesize that Evening Type persons may be predisposed to the sleep difficulties and functional impairments caused by the delayed weekend sleep pattern.

To better understand the direct impacts of a delayed weekend sleep pattern, we conducted a field experiment using a within-subject, counterbalanced design in which subjects' sleep-wake schedule at home were manipulated with and without a delay during the weekend. We hypothesized that: 1) subjects would be less sleepy and take longer to fall asleep on the Sunday night following the delayed weekend sleep pattern; 2) subjects would be sleepier and perform poorly on cognitive tests on the Monday morning following the delayed schedule; and 3) deficits would be greater in Evening Type individuals.

Method

Subjects

Subjects were recruited from The City College of New York and Columbia University in New York City with flyers. Potential subjects completed a survey for medical and sleep history and were interviewed by a graduate student to determine their qualification for participation. No standard diagnostic instrument was used for the subject screening. Inclusion criteria were:

1) aged 18 to 35 years old
2) on a regular shift with a regular sleep-wake schedule
3) napping less than 2 hours per week
4) non-smoker
5) without a history of and not currently troubled by a sleep disorder, major medical illness, neurological or psychiatric disorder.

Forty-six potential subjects were initially included in the study. Sixteen of them discontinued due to either difficulty in following the designated sleep-wake schedule, failing to call in to report their schedule, or dropping out for unknown reasons. Thirty subjects (5 males and 25 females), between the ages of 18 and 31 (mean = 22.3 years of age), completed the study. Five of them were Morning Type, 24 were Neither Type, and only one was Evening Type. Their average weekday sleep-wake schedule was 11:31 p.m. to 7:21 a.m., with an average total time in bed (TBT) of 7.8 ± 1.0 hours. Their average weekend sleep-wake schedule was 12:14 a.m. to 9:04 a.m., with an average TBT of 8.8 ± 1.1 hours.

The experimental protocol was approved by the Institutional Review Board of the City College of New York. A written informed consent was obtained from each subject. Subjects were paid $40 upon the completion of the study as compensation for their time and efforts.

Procedures

Prior to the study, each subject completed a Morningness/Eveningness (M/E) Questionnaire to assess their circadian type (see Measurements section for a description of the questionnaire). A sleep-wake schedule for the study was designated for each subject according to his or her reported habitual bedtime and wake-up time. For subjects whose sleep-wake schedule varied day to day due to job or school schedule, the earliest wake-up time required was taken as the designated wake-up time while the TBT was set to approximate the habitual TBT. However, the designated TBT were set no shorter than 7 hours and no longer than 9 hours. For our sample, the average designated bedtime was 11:21 p.m. and the average wake up time was 7:11 a.m. The average designated TBT was 7.8 ± 0.7 hours, with a range from 7 to 9 hours.

The study was a field experiment in which all the experimental procedures were conducted in their regular environments. Subjects were told that the purpose of the study was to "assess the effects of sleep schedule change on sleep and daytime functioning". In order to avoid subjects' expectation effect, no information regarding the expected results was revealed to the subjects. Throughout the 3-week period of the study, subjects slept at home following specific sleep-wake schedules. Subjects were asked to refrain from drinking alcohol and taking naps. Caffeine consumption was limited to one cup or can of caffeinated drink per day before noon. To enhance the subjects' reliability in following the designated procedures, subjects were provided with a detail checklist to follow. Also, subjects were called by an experimenter at least 3 times a week to remind them of the experimental procedures and to answer questions.

The experiment consisted of one pre-experimental week and two experimental weeks. During the pre-experimental week, subjects followed their designated sleep-wake schedule everyday to stabilize their sleep-wake cycle. In order to keep track of their sleep-wake schedule, they were required to keep sleep logs and to call into an automatic time-stamped voice mail system everyday right before going to bed and right after waking up. Subjects who failed to make the phone call or whose call-in time exceeded a 30-minute range from the designated schedule for more than once were asked to repeat the pre-experimental week or were dropped from participation. Three of the subjects had repeated the pre-experimental week.

The two experimental weeks were comprised of one baseline (BL) week and one delayed-sleep (DS) week. The sequence of the two conditions was counterbalanced across subjects. Fifteen subjects followed each sequence. Throughout the BL weekdays and weekend, subjects followed their designated sleep-wake schedules. During the weekdays of the DS week, the designated sleep-wake schedule was followed. On Friday and Saturday of the DS week, bedtime and wake-up time were delayed by two hours to simulate the delayed weekend sleep pattern. Also, subjects were required to call in the voice mail system and to keep sleep logs everyday during both experimental conditions.

On Sunday night, subjects were asked to rate their sleepiness level with the Stanford Sleepiness Scale (SSS; see Measurements section for description) at five points in time: three hours, two hours, one hour, and 30 minutes before bedtime and right before going to bed. Also, they were asked to complete a visual analog mood scale (VAMS; see Measurements section for description) before going to bed. On Monday morning, subjects filled out a VAMS right after waking up and rated their sleepiness again at five points in time: at awakening and at 30 minutes, one hour, two hour, and three hours after wake-up-time. In addition, an experimenter called the subjects on the telephone at about 5 minutes after waking up for the administration of a Word List Memory Test (WLMT; see Measurements section for description) and a Control Oral Word Association test (COWA; see Measurements section for description). Subjects were asked to make sure the environment was not noisy or distracting before the test administration started.

Measurements

Morningness/Eveningness Questionnaire (M/E Questionnaire).

The M/E Questionnaire (Horne & Ostberg, 1976) is a self-rating scale that consists of 19 multiple-choice questions regarding the individual's preferred sleep-wake time and the time of the day when the individual functions at his/her best (e.g., "You wish to be at your peak performance for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day, and considering only your own "feeling best" rhythm, which one of the four testing times would you choose"). The questionnaire classified individuals into Evening Type (score between 16 and 41) – people who function at best in the evening, Morning Type (score between 59 and 86) – people who function best in the morning, and Neither Type (score between 42 and 58) – people who fall in between the two extreme types.

Stanford Sleepiness Scale (SSS). SSS is a 7-point rating scale in which higher points on the scale describe an increasing level of sleepiness (Hoddes, Zarcone, Smythe, Phillips & Dement, 1973). Subjects were instructed to circle one of seven numbered statements that best described their level of alertness or sleepiness (e.g. from "1-feeling active, vital, alert, wild awake" to "7-almost in reverie, cannot stay awake, sleep onset appears imminent"). Rating on the scale has been shown to be elevated by one night of sleep deprivation and to return to the baseline after a recovery night (Hoddes, et al., 1973).

Visual Analog Mood Scale (VAMS). VAMS is a subjective rating scale for mood status. It required subjects to indicate their mood status on 12 separate mood-related descriptions (e.g. "active", "tense", "sad", "happy") by writing a vertical mark on a 100-mm horizontal line with two poles labeled "very little" and "very much". The length from the left end of the horizontal line to the point of the mark was measured in millimeter as the score for each item.

Cognitive Tests. The selection of cognitive measures on Monday morning was limited by the feasibility of administration by phone and the time constraint (i.e. subjects needed to leave their houses for school or work soon after they woke up on Monday morning). A word-list memory test (WLMT) and the Controlled Oral Word Association test (COWA) were chosen for the study.

The WLMT consists of a free recall trial of 24 words conducted through telephone. The words were read by the experimenter in a rate of approximately two seconds per word. Subjects were asked to recall as many words as they could immediately after the words were presented. The words were taken from the equivalent forms of the Busche Selective Reminding Test (see Spreen & Strauss, 1991). Factors affecting performance on immediate recall of a word-list include short-term verbal memory and immediate span of attention (see Lezak, 1995). These abilities are important for acquiring verbal information, and therefore are crucial for school learning. Also, word-list free recall has been reported to be impaired by one night of sleep deprivation (Williams, Gieseking, & Lubin, 1966). Thus, it was chosen to measure subjects' cognitive functioning on Monday morning.

The COWA test consists of two word-naming trials conducted through the phone. Subjects were given one minute to generate as many words as possible that begin with a given letter of the alphabet (e.g., C, F), excluding proper nouns, numbers, and the same word with a different suffix. The number of words generated was the score. In addition to the oral production of spoken words, performance on this test is associated with mental flexibility and divergent intelligence (see Lezak, 1995). These domains of cognitive functioning are also important for school and work performance. Also, Horne (1988) has demonstrated that 32-hour sleep deprivation lead to poor performance on a similar test. Therefore, it was selected to measure subjects' cognitive ability on Monday morning.

Data Analysis

Repeated measure t-tests comparing the two conditions were performed on all the measures. Effect-size was also calculated for each significant or near-significant comparison (Cohen, 1988). In addition, difference scores for all measures were calculated by subtracting data obtained from BL condition from data obtained from DS condition. Pearson Correlation Coefficients were performed between the M/E score and the difference scores to test the relationships between circadian type and the impacts of delayed weekend sleep pattern. Because of misunderstanding of the instructions or experimenter errors, missing data were found in the following measures: SSS ratings from one subject, Monday morning VAMS from three subjects, Sunday night VAMS from two subjects, sleep logs from three subjects, and cognitive tests from one subject. The subjects' data on the particular measure with missing data were excluded, but their data on the other measures were included for the analysis.

Results

Sunday Night

On Sunday night in the DS condition, subjects rated themselves less sleepy on the SSS compared with the BL condition at 30 minutes before bedtime and right at bedtime, with medium effect-sizes. At 30 minutes before bedtime, the average SSS ratings were 3.7 ± 1.3 for the BL condition and 3.1 ± 1.5 for the DS condition ($t[28] = -2.10$, $p < .05$; $d = 0.55$). At bedtime, the average SSS ratings were 4.3 ± 1.6 for the BL condition and 3.6 ± 1.8 for the DS condition ($t[28] = -2.31$, $p < .05$; $d = 0.61$). There were no SSS differences between the two conditions three, two and one hour before bedtime (see Appendix 1 and Figure 1) VAMS rating on "sleepy" at bedtime was also lower in the DS condition (63.9 ± 25.2 mm.) than in the BL condition (48 ± 30.6 mm.), with a medium effect-size ($t[27] = -2.27$, $p < .05$; $d = 0.61$). However, none of the other VAMS items on Sunday night showed difference between the two conditions (see Appendix 2).

Table 1 shows the data and statistical results from the sleep log on Sunday night. None of the subjective sleep parameters on Sunday night were different between the two conditions. However, there are near significant trends of longer sleep onset latency (SOL) with a medium effect-size and shorter total sleep time (TST) with a small effect-size in the DS condition compared to the BL condition. The average subjective SOL were 13.0 ± 15.9 min. for the BL condition and 19.7 ± 28.0 min. for the DS condition ($t[26] = 1.81$, $p = .08$; $d = 0.50$). The average subjective TST were 465.7 ± 39.4 min. for the BL condition and 454.0 ± 44.1 min. for the DS condition ($t[26] = -1.78$, $p = .09$; $d = 0.49$).

Monday Morning

Figure 2 showed the results of cognitive tests on Monday morning. Subjects generated significantly more words on the COWA in the BL condition (21.9 ± 7.1 words) than in the DS condition (18.1 ± 6.3 words) with a large effect size (t[28] = -3.49, p < .005; d = 0.92). On the WLMT, subjects memorized significantly more words in the BL condition (9.0 ± 2.6 words) than in the DS condition (7.7 ± 2.3 words) with a medium effect size (t[28] = -2.71, p < .05; d = 0.71).

On the mood scale of Monday morning, subjects rated themselves less "alert", more "sleepy", more "irritable", more "angry", and overall in a worse mood following the DS weekend compared to the BL weekend, with medium to large effect-sizes. Table 2 shows the mean ratings, standard deviations, results of t-tests for the VAMS data on Monday morning. In contrast, sleepiness ratings on the SSS on Monday morning were not different between the two conditions (see Figure 3 and Appendix 3).

Morningness/Eveningness (M/E)

The average M/E score for the subjects was 52.1 (SD = 6.6) with a maximum score of 66 and a minimum score of 39. M/E score was shown to be significantly correlated with the difference scores on two variables, the level of sleepiness (r = .39, p < .05) and the level of anger (r = .43, p < .05) as measured by the VAMS on Sunday nights. The greater the "Eveningness" of a subject the greater the effect of the delayed weekend sleep pattern on sleepiness and anger ratings on Sunday night. Near-significant correlations were also found between M/E score and the difference scores of sadness on Sunday night and the performance on WLMT on Monday morning (r = .37, p = .054 and r = .31, p

= .098, respectively). Subjects with an Evening tendency tended to be less sad on Sunday night and to remember fewer words on the WLMT on Monday morning in the DS week compared to the BL week.

Discussion

This field study has shown that an imposed two hour delay in bedtime and wake-up times on Friday and Saturday nights produces decreased subjective sleepiness and near significant prolonged time in falling asleep at the habitual retiring time on Sunday night and impaired mood and cognitive functioning on Monday morning. This is the first study, to our knowledge, that employed an experimental design to demonstrate a direct causal relationship of this maladaptive sleep pattern with decrease in daytime functioning and potential sleep problems.

Another purpose of the present study was to test the hypothesis that Evening Type individuals are predisposed to a larger deficit from the phase delay of the delayed sleep pattern. The attempt to test this hypothesis failed because our sample contained only one Evening Type subject. Since Evening Type individuals have been shown to have more irregular sleep-wake schedule (Ishihara, Miyasita, Inugami, Fukuda & Miyata, 1987), our inclusion criterion of being on a regular sleep-wake schedule and the experimental requirement to follow a designated sleep-wake schedule for three weeks may have excluded the majority of the Evening Type individuals. Within our sample, M/E score was shown to have only limited predictive power. The hypothesis that Evening tendency individuals are more prone to be effected by this delayed sleep pattern is not supported. This issue requires further investigation.

The findings that a delayed weekend sleep pattern produces reduced sleepiness on Sunday night and decreased functioning on Monday morning suggest the possibility that a phase delay in circadian rhythms is responsible. Two features of circadian regulation may account for this drift in phase. First, the greater than 24 hour period length of endogenous circadian rhythms may produce a progressive delay in the timing of the rhythms as seen in free running conditions. Second, the two hour delay in wake-up time in the present study prevents exposure to time cues in the morning that would reset or phase advance the endogenous circadian oscillator. While this model is capable of explaining the current findings, a model of homeostatic regulation of sleep propensity also offers a plausible alternative explanation (Borbely, 1994). The decreased sleepiness on Sunday night may be due to the late wake-up time Sunday morning shortening the duration of waking on Sunday in the DS condition. This reduction in prior wakefulness would result in both a reduced level of process S at bedtime as well as reduced discharge of sleep Sunday night. Similarly, the effects on mood and cognitive functioning on Monday morning may in turn be caused by the marginally poorer sleep on Sunday night in the DS condition. In order to differentiate the alternative hypotheses, more extensive measures of circadian rhythmicity, such as body temperature or melatonin markers in the constant routine are needed to establish that a phase shift is responsible for the deficit seen.

A previous study has shown that college students with delayed weekend sleep pattern experienced sleep onset difficulty during weekday nights (Lack, 1986). Although the current study showed only medium effects of the delayed schedule in lowering sleepiness and increasing SOL on Sunday night, four of the subjects reported substantial increases of SOL of more than 30 minutes. The phase delay does not produce a greater increase in SOL perhaps because most people are generally partially sleep deprived, therefore they can easily fall asleep when given the opportunity. The average amount of TBT for the study was 7.8 hours. This sleep duration may not be adequate for individuals of this age (Strauch & Meier, 1988).

In addition, in the previous survey, only 17% of the subjects were bothered by the delayed weekend sleep pattern (Lack, 1986). It is possible that some individuals are not as affected by the weekend delayed sleep. The relatively weak predictive power of M/E may also reflect our sampling problem with all but one subject being Neither and Morning Types.

The findings of impaired cognitive performance and mood status on Monday morning is consistent with the survey findings of negative correlations between school performance and the amount of bedtime delay over the weekend (Allen, 1992; Kowalski & Allen, 1995). This suggests that the delayed weekend sleep pattern can have a direct impact on school or job performance. The exploration of possible coping strategies for these morning effects is needed.

One potential problem of the current study is that the subjects were not blinded to the manipulation of their sleep-wake schedule. They were aware of the conditions they were in. The expectation of the subjects could have contributed to the differences in subjective ratings on their sleepiness level and mood status. Other methodological limitations due to the features of the field experiment include the lack of control over the subjects' sleep-wake schedule and daytime behaviors (e.g., caffeine consumption), and nonstandardized environments and activities subjects engaged in while the assessments were conducted. Further studies conducted in well-controlled laboratory settings with more objective measures and elimination of time cues will help avoid expectation effects and generate more reliable data.

Table 1. Measures of sleep log on Sunday night: Comparison between Baseline and Delayed Sleep conditions (N = 27)

	Baseline		Delayed			
Variable	**Mean**	**SD**	**Mean**	**SD**	*t*	*p*
SOL	13.0	15.9	19.7	28.0	1.81	.08
WASO	1.1	2.0	0.7	1.3	-1.33	.20
TBT	476.7	37.5	474.4	38.1	-0.66	.52
TST	465.7	39.4	454.0	44.1	-1.78	.09
SQ	5.6	1.2	5.6	1.1	0.00	1.00
DW	3.3	1.4	3.4	1.5	0.14	.89

SOL = sleep onset latency (min.); WASO = wake time after sleep onset (min.); TBT = total time in bed (min.); TST = total sleep time (min.); SQ = subjective rating of sleep quality; DW = subjective rating of difficulty to wake up.

Table 2. Visual Analog Mood Scale ratings on Monday morning: Comparison between Baseline and Delayed Sleep conditions (N = 28)

	Baseline		Delayed				Effect-
Item	Mean	SD	Mean	SD	*t*	*p*	Size (d)[a]
Alert	49.0	24.7	35.0	18.3	-2.49*	.02	0.66
Sad	15.0	19.4	19.6	18.8	1.01	.32	--
Tense	29.1	24.4	34.2	22.0	0.83	.41	--
Effort	57.8	24.9	44.6	26.8	1.97	.06	--
Happy	44.6	25.5	37.4	18.9	-1.22	.23	--
Hungry	38.1	30.6	34.6	26.3	-0.48	.63	--
Weary	41.0	31.8	49.4	25.5	1.38	.18	--
Irritable	30.7	30.5	46.0	29.0	2.75*	.01	0.74
Sleepy	47.3	29.2	68.0	21.2	3.25***	.00	0.87
Angry	18.6	21.0	30.3	26.0	2.21*	.04	0.59
Sexual	17.8	19.1	17.0	18.8	-0.29	.78	--
Overall	59.7	23.6	44.5	18.4	-2.78*	.01	0.74

*$p < .05$; **$p < .01$; ***$p < .005$

[a] Effect sizes were only calculated for variables with significant results.

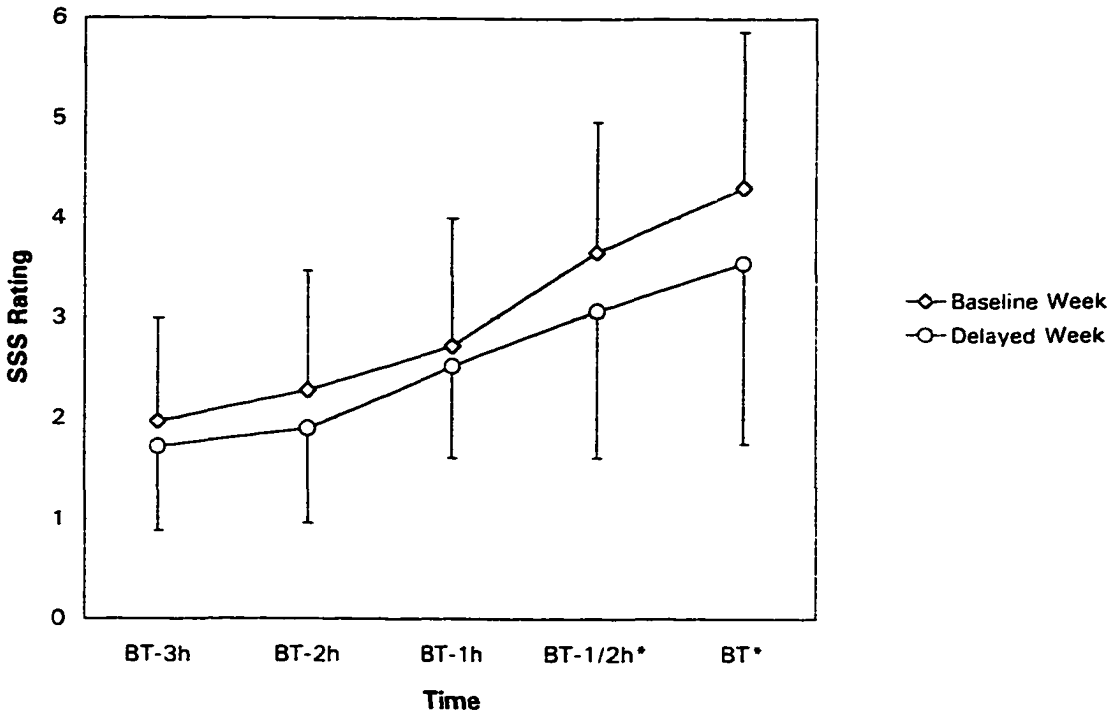


Figure 1. Means of Stanford Sleepiness Scale (SSS) ratings from 3 hours before bedtime to bedtime on Sunday night: comparisons between Baseline and Delayed Sleep conditions. As indicated, subjects rated themselves less sleepy at half hour before bedtime and right at bedtime on Sunday night of the Delayed Sleep week comparing with the ratings during the Baseline week.

(BT = bedtime; * $p < .05$)

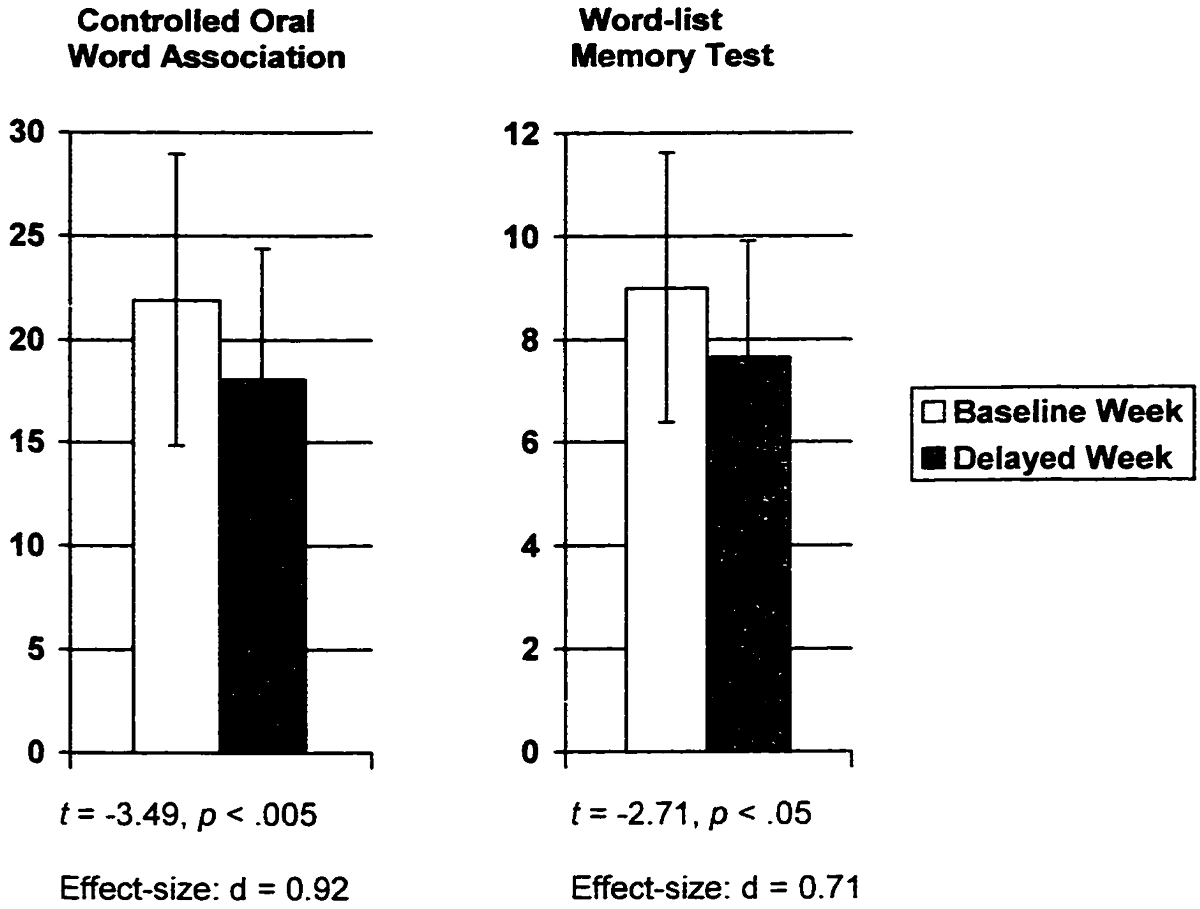


Figure 2. Cognitive performance (Mean ± SD) on Monday morning: comparisons between Baseline and Delayed Sleep conditions. Subjects performed significantly better during Baseline condition on both Controlled Oral Word Association and Word-list Memory Test.

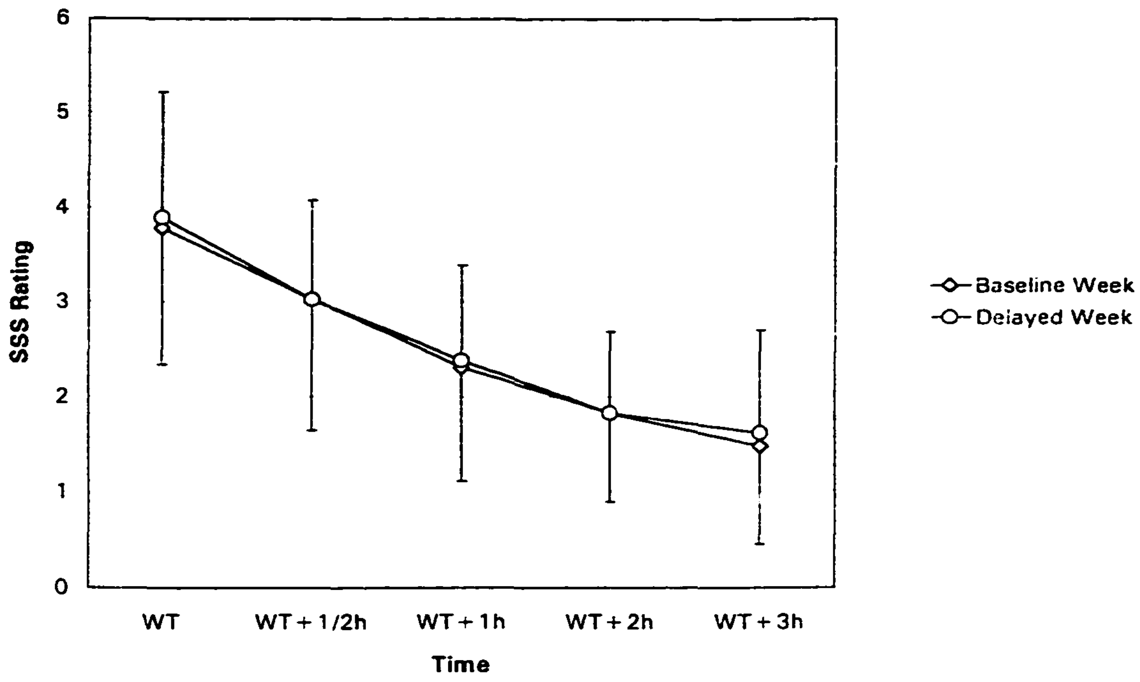


Figure 3. Means of Stanford Sleepiness Scale (SSS) ratings from wake-up time to 3 hours after wake-up time on Monday morning: comparison between Baseline and Delayed Sleep conditions. There were no significant differences between the ratings of the two conditions at any points of time.

(WT = wake-up time)

Appendix 1. Table for Stanford Sleepiness Scale ratings on Sunday night:

Comparison between Baseline and Delayed Sleep conditions (N = 29)

	Baseline		**Delayed**			
Time	**Mean**	**SD**	**Mean**	**SD**	*t*	*p*
Bedtime-3hrs	2.0	1.0	1.7	0.8	-1.13	.27
Bedtime-2hrs	2.3	1.2	1.9	0.9	-1.83	.08
Bedtime -1hr	2.7	1.3	2.5	0.9	-0.92	.36
Bedtime -1/2hr	3.7	1.3	3.1	1.5	-2.10*	.04
Bedtime	4.3	1.6	3.6	1.8	-2.31*	.03

*$p < .05$

Appendix 2. Table for Visual Analog Mood Scale ratings on Sunday night: Comparison between Baseline and Delayed Sleep conditions (N = 28)

	Baseline		**Delayed**			
Item	**Mean**	**SD**	**Mean**	**SD**	***t***	***P***
Alert	45.1	23.4	46.8	28.6	0.29	.78
Sad	25.4	25.8	16.1	17.9	-1.60	.12
Tense	25.1	23.4	21.1	20.9	-0.91	.37
Effort	42.2	26.9	35.1	27.7	-1.20	.24
Happy	43.9	23.0	49.1	26.6	0.76	.46
Hungry	25.6	26.5	23.8	24.0	-0.30	.77
Weary	48.7	29.2	43.6	30.9	-0.78	.44
Irritable	33.2	28.2	27.9	28.8	-0.82	.42
Sleepy	63.9	25.2	48.0	30.6	-2.27*	.03
Angry	25.4	28.7	21.3	25.4	-0.87	.39
Sexual	23.6	21.4	24.1	21.6	0.12	.91
Overall	55.3	19.5	57.2	25.0	0.35	.73

*$p < .05$

Appendix 3. Table for Stanford Sleepiness Scale ratings on Monday morning:

Comparison between Baseline and Delayed Sleep conditions (N = 29)

	Baseline		**Delayed**			
Time	**Mean**	**SD**	**Mean**	**SD**	*t*	*p*
WT	3.8	1.4	3.9	1.3	0.35	.73
WT + 1/2hr	3.0	1.4	3.0	1.1	0.00	1.00
WT + 1hr	2.3	1.2	2.4	1.0	0.27	.78
WT + 2hrs	1.8	0.9	1.8	0.9	0.00	1.00
WT + 3hrs	1.5	1.0	1.6	1.1	0.68	.50

WT = wake-up time

Experiment 2: Treatment of weekend sleep phase delay with melatonin

Abstract

Young adults tend to delay their sleep-wake schedule during the weekend. This sleep pattern has been reported to lead to sleep initiation difficulties and morning functional impairments on weekdays when individuals switch back to their regular sleep schedule (Allen, 1992; Kowalski & Allen, 1995; Lack, 1986). These effects suggest a mild phase delay of endogenous circadian rhythms caused by the delayed sleep pattern. The present study tested the effects of melatonin administration as a means of preventing the Sunday night-Monday morning phase delay following a delayed weekend sleep pattern. The sample included ten subjects (2 males and 8 females), between the ages of 18 and 29, recruited from college settings. A within-subject, counterbalanced design was used in which each subject participated in the placebo and melatonin conditions. In each condition, subjects slept in the lab for four consecutive nights from Friday to Monday. Subjects' sleep-wake schedules were delayed by 2 hours on Friday and Saturday to simulate the delayed weekend sleep pattern. A pill containing either 6-mg melatonin or placebo was administered double blind on Sunday late afternoon. Subjects' levels of sleepiness, vigilance and mood status were tested on Sunday evening. Their sleep on Sunday night was recorded by nocturnal polysomnography. On Monday morning, their levels of sleepiness and mood status were rated and a brief battery of cognitive tests was administered. In addition, subjects' onset time of endogenous melatonin secretion was measured with dim-light salivary melatonin onset (DLSMO) on

Friday and Monday nights to assess the phase shift of the endogenous circadian rhythm over the weekend.

Compared with the placebo condition, subjects in the melatonin condition rated themselves sleepier and demonstrated a shorter sleep onset latency on Sunday night, and rated themselves less sleepy and had a better mood on Monday morning. DLSMO also indicated significant phase delay in the melatonin rhythm in the placebo condition, but not in the melatonin condition. These findings suggest that a delayed weekend sleep pattern causes a delay in endogenous circadian rhythms. In addition, administration of melatonin on one night is capable of counteracting the drift of circadian rhythms and preventing the adverse effects of a weekend phase delay. The sedating effect of melatonin as a potential side effect was also evaluated. In addition, problems in subject selection that may have limited the beneficial effects of melatonin administration are discussed.

Key words: Sleep; Human; Circadian Rhythms; Melatonin

Introduction

Human sleep propensity is regulated by the interactions of two different processes: a homeostastic process and a circadian process (see Borbely, 1988). The homeostastic process of sleep is determined by the duration of prior sleep and waking. The longer the amount of prior sleep, the less sleep propensity at a given moment. The longer the prior wakefulness, the greater the sleep propensity. On the other hand, the circadian process, which is independent of the amount of prior sleep and waking time, regulates a recurrent cycle of sleep-wake propensity in a near-24-hour rhythm.

The endogenous circadian process regulates not only the timing of sleep, but also rhythmic changes in various physiological variables, such as core body temperature, melatonin and cortisol secretion. The endogenous circadian oscillators that regulate the various rhythms are located in the suprachiasmatic nuclei (SCN) of the hypothalamus (Eastman, Mistlberger, & Rechtschaffen, 1984; Moore & Eichler, 1972; Ralph, Foster, Davis & Menaker, 1990). Normally, light-dark information reaches the SCN and synchronized the endogenous circadian rhythms with the 24-hour environmental light-dark cycle through the retinohypothalamic tract (RHT) – a neural pathway projected from the retina into the hypothalamus within or near SCN (Sadun, Schaechter & Smith, 1984). However, when the light-dark information and other time cues are deprived, the intrinsic rhythm of human circadian regulation is approximately 24.2 hours (Campbell, Dawson & Zulley, 1993; Czeisler et al., 1995; Dijk &

Czeisler, 1995). Thus, there is a tendency for circadian rhythms in general, and the sleep-wake rhythm in particular, to drift later in time. When the sleep-wake rhythm and underlying circadian rhythms drift to a phase delayed position relative to the desired sleep-wake schedule, sleep problems occur.

This condition, called Delay Sleep Phase Syndrome (DSPS), has been well described (Alvarez, Dahlitz, Vignau & Parkes, 1992; Ozaki, et al., 1988; Weitzman, et al., 1981). Patients with DSPS often complain of difficulty initiating sleep at the desired bedtime and difficulty waking up in the morning for school or work. However, when they are allowed to choose their sleep-wake schedule, such as during the weekend or on vacation, they will delay their bedtimes and wake-up times and will report no problem with initiating sleep or with waking up. It has been suggested that patients with DSPS may have a relatively weak ability to phase advance their circadian system, and therefore, their endogenous circadian rhythm is chronically delayed in relation to the environmental light-dark cycle (Czeisler, et al., 1981).

The present study targets a transient and milder form of sleep phase delay in young adults. The common practice of going to bed late and getting up late during the weekend creates a problem falling asleep, as well as a problem waking in the morning. Several survey studies have documented a delayed weekend sleep pattern in young adults and its associations with sleep difficulty and poor school performance (Allen, 1992; Kowalski & Allen, 1995; Lack, 1986). A field experiment conducted by our laboratory also demonstrated decreased subjective sleepiness on Sunday night and functional impairments on Monday morning following a single weekend of an imposed 2-hour delayed sleep-wake schedule (Yang, Spielman, Martinez, Cordero, & Nagata, 1997; also see Experiment 1 of this dissertation).

It has been proposed that the mechanism responsible for this condition implicates the circadian regulation system (Lack, 1986; Valdez, 1996). Because of the greater than 24 hour period length of the endogenous circadian rhythms, a delayed weekend sleep pattern can produce a progressive delay in the timing of the rhythms as seen in the "free running" condition. Also, the delay in the wake-up time during the weekends can prevent exposure to time cues in the morning that normally reset or phase advance the endogenous circadian oscillator.

Although this weekend sleep phase delay may be milder in severity and more transient in duration compared to DSPS, it is much more common and may precipitate DSPS in individuals who are predisposed to a phase delay. The most direct way to prevent the weekend sleep phase delay is to avoid staying up late and getting up late during the weekend. However, there are occasions when one simply cannot avoid a delayed sleep pattern due to social, academic or work demands. Another route to prevent the weekend sleep phase delay or to minimize it is to counteract the phase delay of endogenous circadian rhythm by advancing circadian rhythms with environmental stimuli.

Phase shifts of the endogenous circadian rhythms can be produced by a number of environmental stimuli. Among these stimuli, light is the most potent.

There is a relationship between the timing of light exposure and the extent and direction of the phase shift induced. This relationship can be plotted as a Phase Response Curve (PRC). In general, light exposure in late subjective day and early subjective night produces a phase delay, and light exposure in late subjective night and early subjective day produce a phase advance (see Czeisler, 1995). Therefore, the timing for the bright light to be most effective in advancing the endogenous circadian rhythm is in the early morning, just prior to and just after the habitual time of rising. However, this is not a practical approach since most people have difficulty getting up around the habitual arising time on the weekend when they have gone to sleep later than usual.

Another stimulus that possesses phase-shifting properties is exogenously administered melatonin. Melatonin is a hormone produced by the pineal gland during the hours of darkness. The primary function of melatonin is believed to be communicating information of daily light-dark cycle to body physiology (Cardinali & Pevet, 1998). Although there are still some debates (Czeisler, 1997), the PRC for melatonin has recently been described and is about 180 degrees out of phase with the effects of light (Lewy, Ahmed, Jackson, & Sack, 1992; Zaidan, et al., 1994). Thus, the most effective timing of melatonin administration to advance circadian rhythms is late subjective day. The administration of melatonin at this time may be a practical way to treat the weekend sleep phase delay phenomena.

In previous studies, near physiological doses (0.5 mg) to low pharmacological doses (2 to 5 mg) of melatonin in the late afternoon and early evening have been shown to induce phase advances of endogenous circadian rhythm, indicated by the melatonin, temperature and sleep-wake rhythms (Arendt, Borbely, Franey, & Wright, 1984; Deacon & Arendt, 1995; Deacon, English, & Arendt, 1994; Krauchi, Cajochen, Mori, Hetsch, & Wirz-Justice, 1995; Wirz Justice, Krauchi, Cajochen, Mocaer, & Defrance, 1996). Five mg of melatonin administered in the evening for 2 to 6 weeks has also been shown to decrease sleep onset latency and to advance the sleep-wake rhythm measured by subjective sleep logs, actigraphy, nocturnal polysomnography, and ambulatory polygraphic recording (Dagan, Yovel, Hallis, Eisenstein & Raichik, 1998; Dahlitz et al., 1991; Nagtegaal, Kerkhof, Smits, Swart & van der Meer, 1998; Oldani, Ferini-Strambi, et al., 1994). In addition, melatonin administration has also been used, with some success, to alleviate maladaptation to shift work (Folkard, Arendt & Clark, 1993; Sack & Lewy, 1997) and jet lag (Arendt, et al., 1987; Comperatore, Lieberman, Kirby, Adams & Crowley, 1996). For example, 5 mg melatonin administered daily at 6:00 p.m. for 3 days prior to an eastward flight over 8 time zones, combined with bedtime administration of 5 mg melatonin for 4 days after arrival has been showed to facilitate the adaptation to new time zone, indicated by subjective (jet lag ratings, sleep ratings, and mood ratings) and objective (actigraphy, endogenous melatonin and cortisol) measures.

These findings suggest that melatonin administration may be a potential treatment for the weekend sleep phase delay phenomena.

In addition to its circadian rhythm shifting properties, melatonin administration has also been shown to possess an acute sedating property. When given during the daytime, it increases the level of subjective fatigue and sleepiness (Cajochen, et al., 1996; Deacon et al., 1994; Deacon & Arendt, 1995), decrease sleep onset latency (Nave, Peled & Lavie, 1995; Reid, van den Heuvel & Dawson, 1996; Tzischinsky and Lavie, 1994), and impair cognitive performance (Deacon & Arendt, 1995; Rogers, Phan, Kennaway, & Dawson, 1998) a couple of hours after the administration. This acute sedating effect can be a potential side effect when melatonin is given in the late afternoon as a strategy to advance endogenous circadian phase.

The present study's aim is to demonstrate the delay in endogenous circadian rhythm following delayed weekend sleep pattern, and to explore the utilization of melatonin administration on one night to counteract the phase delay and to prevent the behavioral consequences produced by the phase delay. In the present study, the delayed weekend sleep pattern was simulated on the weekends in the lab by having subjects go to bed and get up two hours later than their regular sleep-wake schedule for two consecutive nights. With a double blind placebo-controlled, crossover design, a pill containing either 6 mg of melatonin or placebo was given to subjects late Sunday afternoon. The amounts of phase shift in the endogenous circadian rhythm were measured by dim-light salivary melatonin onset (DLSMO), a marker of the onset of endogenous melatonin secretion (Carskadon, Acebo, Richardson, Tate & Seifer. 1996; Lewy & Sack, 1989; McIntyre, Norman, Burrows & Armstrong, 1987; Nagtegaal, Peeters, et al., 1998; Voultsios, Kennaway & Dawson, 1997). Subjective sleepiness, mood status, and cognitive functioning on Sunday night and Monday morning were also measured by subjective ratings and cognitive tests. Sleep on Sunday night was recorded with polysomnography and rated on a sleep log. The study also measured the sedating effect of melatonin administration as a potential side effect by periodically measuring subjective sleepiness with rating scales and by testing the level of alertness with a computerized vigilance test.

Methods

Subjects

Subjects were recruited from The City College of New York by flyers and public announcements. Prior to the experiment, potential subjects were interviewed by a graduate student and filled out a survey questionnaire for sleep and medical history. No standard diagnostic instrument was given for the screening. They were also asked to complete the Morningness-Eveningness Questionnaire, a 19-item self-rating scale that survey the time of the day when an individual functions at the best (Horne & Ostberg, 1976). It classified individuals into Evening Type (score between 16 and 41) – people who function at best in the evening, Morning Type (score between 59 and 86) – people who function best in the morning, and Neither Type (score between 42 and 58) – people who falls in between the two extreme types. Inclusion criteria for participation were as follow:

1) 18 to 30 years of age.
2) Evening Type (< 42) or Neither Type (between 42 and 58) as measured by the Morningness-Eveningness Questionnaire. This criterion was instituted because Evening Type has being demonstrated to be associated with a delayed circadian phase, and therefore may be prone to developing the weekend sleep phase delay (Bailey & Heitkemper, 1991; Breithaupt & et al., 1978; Clodore, Foret, & Benoit, 1986; Hall, Duffy, Dijk, & Czeisler, 1997).
3) Non-shift worker, no recent travel across time zone and on a regular sleep-wake schedule.
4) Non-smoker, not using psychoactive drugs or medicines that affect sleep.
5) No history or current sleep, medical, neurological, or psychiatric disorder.
6) Female subject with no history or current premenstrual dysphoric disorder (PMDD) based on the research criteria from DSM-IV (American Psychiatric Association, 1994). Female potential subjects with PMDD were excluded because the endogenous melatonin rhythm

has been shown to vary at different stages of the menstrual cycle (Parry, Berga, Mostofi, Klauber, & Resnick, 1997).

A total of 19 potential subjects initiated the study. Nine of these individuals either withdrew because of difficulty following the designated sleep-wake schedule, or were dropped because of failing to call in to report their bedtime and wake-up time.

Ten subjects (2 males and 8 females), between the ages of 19 and 29 (mean = 22.1 years), completed the study. Their reported average weekday sleep-wake schedule was 11:55 p.m. to 7:55 a.m. and average weekend schedule was 1:23 a.m. to 9:56 a.m.. Their average habitual total time in bed (TBT) during weekday was 8.0 ± 0.9 hours and habitual weekend TBT was 8.6 ± 1.4 hours. All of the subjects completing the study were Neither Type (mean M/E score = 47.7, SD = 3.7).

The experimental protocol was approved by the Institutional Review Board at the City College of New York. A written informed consent was obtained from each subject. Subjects were paid $200 upon the completion of the study as compensation for their time and efforts.

Procedures

The experiment was a counterbalanced within-subject design, with one pre-experimental week followed by two experimental weeks: one melatonin condition and one placebo condition. Each week started on a Tuesday night and ended the next Tuesday morning. The sequence of the two conditions was counterbalanced across subjects to eliminate the sequence effect. Throughout the 3-week period of the study, subjects were required to keep a daily sleep log and to refrain from drinking alcohol and taking naps. Caffeine consumption was limited to one cup of coffee or one can of caffeinated drink per day before noon.

A sleep-wake schedule for the study was designated for each subject according to his or her reported habitual bedtime and wake-up time. For subjects whose sleep-wake schedule varied from day to day due to job or school schedule, their earliest wake-up time required was taken as the designated wake-up time while the TBT was set to approximate the habitual TBT. However, the designated TBT were set no shorter than 7 hours and no longer than 9 hours. The average designated bedtime for our sample was 11:34 p.m. and average designated wake-up time was 7:35 a.m. The average designated TBT was 8.0 ± 0.4 hours, with a range from 7.5 to 8.5 hours.

Pre-experimental Week

During the pre-experimental week, subjects slept at home and followed the designated sleep-wake schedule for the entire week to stabilize their sleep-wake rhythm. They were required to call an automatic stamped voice mail system everyday right after getting up in the morning and right before going to bed to report their sleep-wake schedule. Subjects who failed to follow the designated sleep-wake schedule for more than once were required to repeat the pre-experimental week or were dropped from the study. Only one of the completed subject repeated the pre-experimental week. At the end of the pre-experimental week and throughout out the experimental weeks, subjects wore a wrist actigraph (Ambulatory Monitoring, Inc., Ardsley, New York) to monitor their sleep-wake timing. Because of technical errors, actigraph data was not analyzed. However, it was used to confirm if the subjects followed the designated sleep-wake schedule at home and was successful in detecting failures of following the designated schedule in 3 potential subjects.

Experimental Weeks

Subjects followed the same experimental procedures for the two experimental weeks except for the content of the pill they took. From Tuesday to Thursday subjects slept at home and continued keeping sleep logs and calling the voice mail system. For nights Friday-Monday, subjects came to the CCNY sleep lab in the evening and stayed overnight. Their sleep-wake schedules in the lab were manipulated to simulate the delayed weekend sleep pattern.

On Friday nights, subjects came to the lab 6 hours before their designated habitual bedtime for the baseline determination of dim-light salivary melatonin onset (DLSMO). The test was conducted from 4 hours before regular bedtime to 1 hour after regular bedtime (see Measurements section for the procedures). Subjects retired 2 hours after their designated habitual bedtime and were awakened 2 hours after their designated habitual wake-up time. They were instructed to stay in bed and to try to fall back to sleep if they woke up before the designated wake-up time. After waking, subjects were kept in the lab for an hour in order to prevent morning light exposure, since people do not usually go right out after waking up during the weekend.

On Saturday nights, subjects came to the lab an hour before their designated habitual bedtime. A practice trial of the cognitive tests (description to follow in Measurements section) was administered in order to orient them to the tests and to limit practice effects. Electrodes were then applied following standard montage to habituate subjects to sleep recording procedure (Agnew, Webb, & Williams, 1966), but no sleep recording was conducted. Subjects were told that the procedure was to habituate them with the sleep recording, and sampling recording might be conducted to check up the equipment. The sleep-wake schedule was the same as Friday night.

On Sunday nights, subjects came to the lab 6 hours before their designated bedtime. A pill containing either 6 mg melatonin (for melatonin condition) or 6 mg mannitol (a biologically inactive substance, for placebo condition) was administered 5.5 hours before their habitual bedtime. This timing was chosen because the melatonin PRC indicates that the phase advance timing for melatonin administration is between approximately 11 to 3 hours before bedtime (CT4 to CT12; Lewy et al., 1992). Since subjects' endogenous circadian rhythm was expected to be mildly delayed on Sunday night, a relatively late timing within the window for phase advance was chosen.

Throughout Sunday evening, subjects' sleepiness ratings on the modified Stanford Sleepiness Scale (SSS; description to follow in Measurements section) were obtained every 30 minutes, and levels of alertness were assessed twice (4.5 hours and 1 hour before bedtime) by the Multiple Vigilance Test (MVT: description to follow in Measurements section). In addition. electrodes were applied for a sleep recording at 2 hours before bedtime. Right before going to bed, a visual analog mood scale (VAMS; description to follow in Measurements section) was administered to assess subjects' mood. Subjects went to bed at their designated bedtime. Nocturnal polysomnographic (NPSG) recordings were conducted throughout the night (see Measurements section for the procedures). Subjects were awakened at their designated wake-up time on Monday morning. The VAMS was administered right after they woke up. After subjects used the bathroom, a short battery of cognitive tests was administered (see Measurements section for description). SSS ratings were also obtained hourly from 1 to 3 hours after they woke up.

Monday late day subjects came back to the lab 6 hours before their designated bedtime for a repeat DLSMO. Subjects' bedtimes were delayed for one hour in order to finish collecting saliva samples for DLSMO test. Subjects were put to bed after the DLSMO test was completed and were awakened at their designated wake-up time.

Throughout the time when the subjects were awake in the lab, illumination level was maintained below 50 lux in order to eliminate the suppressing effects of light exposure on endogenous melatonin secretion (McIntyre, Norman, Burrows, & Armstrong, 1989).

Figure 1 illustrates the experimental procedures and sleep-wake schedule for the two experimental weeks.

Measurements

Dim-Light Salivary Melatonin Onset (DLSMO) Test

The DLSMO test was conducted on Friday and Monday nights in both experimental conditions. Subjects were instructed to come to the lab 6 hours before their designated habitual bedtime. Saliva samples were collected every 30 minutes from 4.5 hours before their designated habitual bedtime to 1 hour past their designated habitual bedtime. At least 3 ml of saliva was collected for each sample. Saliva samples were then centrifuged and stored at -20℃. The amount of melatonin contained in each sample was measured by a double-antibody radioimmunoassay conducted at the biochemical lab of the New York Hospital–Cornell Medical Center (White Plain, New York), following the procedures provided by American Laboratory Products Co. (Windham, NH). Samples were analyzed in duplicate with two separate batches of assay. Samples from the same subject were analyzed by the same batch. The intraassay and interassay coefficients of variation were 4.1 and 8.9%, respectively. The onset time of nighttime salivary melatonin was calculated as the first interpolated point above 4.0 pg/ml melatonin that continued to maintain above the threshold in later samples. This threshold criterion has been validated in previous studies (Carskadon, Acebo, Richardson, Tate & Seifer, 1996; Nagtegaal, Peeters, et al., 1998; Tzischinsky et al., 1995).

Nocturnal Polysomnographic (NPSG) Recording

The NPSG montage included electroencephalogram (EEG) with C3 or C4 referenced to linked mastoids (A1+A2) and O1 or O2 referenced to A1+A2, electro-oculogram (EOG) recorded from outer canthus of both eyes, chin electromyogram (EMG) and electrocardiogram (EKG). Recordings were obtained on a Grass Model 8 polygraph machine with a paper speed of 10 mm/sec. The records were scored manually in 30-second epochs by trained scorers who were blind to the conditions, following the standard scoring system (Rechtschaffen & Kales, 1968). The sleep parameters calculated included total sleep time (TST), sleep efficiency (SE), percentage of wake time after sleep onset (WASO%), percentage of different sleep stages, percentage of total wake time (TWT%), sleep onset latency (SOL; light-out time to the first of 3 consecutive epochs of sleep), onset latencies of different sleep stages, and total number of arousals scored according to the rules from the American Sleep Disorders Association (ASDA, 1992).

Sleep Log

Subjects were required to keep daily sleep logs throughout the three-week experimental period. The log included two parts: one to fill out before going to bed and the other to fill out right after waking up. The evening portion was comprised of questions regarding the activities of the day, such as caffeine consumption, medications taken, and exercise. The morning portion of the log asked questions about the sleep of the previous night, such as lights-out time, sleep onset latency, and time out of bed in the morning. It also included two 7-point rating scales to assess the subjective quality of sleep and the level of difficulty getting up in the morning.

A modified Stanford Sleepiness Scale (SSS)

SSS is a 7-point rating scale in which higher points on the scale describe an increasing level of sleepiness. Rating on the scale has been shown to be elevated by one night of sleep deprivation and to return to the baseline after a recovery night (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973). We modified the procedure of the SSS rating by requiring subjects to sit quietly in a dark room with their eyes closed for one minute before each SSS rating. This procedure was employed in an attempt to eliminate the masking effects of behavioral arousal.

Visual Analog Mood Scale (VAMS)

VAMS is a subjective rating scale for mood status. It required subjects to indicate their mood status on 12 separate mood-related descriptions (e.g. "active", "tense", "sad", "happy") by writing a vertical mark on a 100-mm horizontal line with two poles labeled "very little" and "very much". The scales were scored by measuring the length from the left end of the horizontal line to the point of the mark.

Cognitive Tests

Cognitive tests were selected to measure diverse areas of cognitive abilities which have been shown to be sensitive to sleep loss and are associated with school learning and/or work performance. The cognitive tests administered included the Multiple Vigilance Test (MVT), a nine-choice simple reaction time test, a word-list memory test (WMT), the Controlled Oral Word Association (COWA).

Multiple Vigilance Test (MVT).

MVT is a computerized visual continuous performance test. The task was to detect a target stimulus (a letter H) among non-target figures (a side-way letter H) presented with random inter-stimulus intervals, ranging from 4 to 11 seconds. Subjects were instructed to press the space bar on the keyboard as quickly as possible when a target stimulus was presented. The administration of the test took approximately 30 minutes. A total of 240 stimuli were presented, 60 were target stimuli and 180 were non-target stimuli. Subjects' reaction time, the numbers of misses and false alarms were automatically scored. This type of test is used to assess lapses in attention or vigilance and impulsivity (see Spreen & Strauss, 1991). Also, the reaction time on this test has been shown to be negatively correlated with SSS rating. Also, the number of misses was found to be negatively correlated with Multiple Sleep Latency Test (MSLT) – the standard objective measure for sleepiness, and SSS rating (Hirshkowitz, De La Cueva, & Herman, 1993).

Nine-choice simple reaction time test. The test displayed a 3x3 array of 9 squares on a computer screen that matched the 9 number keys on the number keypad of the computer keyboard. The target was the square that was filled in with red color. Subjects' task was to press the key on the number keypad that corresponded to the red square. They were instructed to press the key as quickly and as accurately as they could. A total of 100 trials were presented. The percentage of correct responses and average reaction time were recorded. The test is used to measure visual-motor coordination, processing speed, and attention. Performance on serial choice reaction time test has been shown to vary over the day, with an initial rise after waking up, followed by a post-lunch dip and a second rise toward the evening (see Colquhoun, 1981).

Word-list Memory Test (WMT). A list of 24 words were presented one at a time on a computer screen in a rate of 3 seconds each word. Subjects were asked to recall as many words as they could immediately after all 24 words were presented. The words were taken from the equivalent forms of the Busche

Selective Reminding Test (see Spreen & Strauss, 1991). Factors affecting performance on immediate recall of a word-list include short-term verbal memory and immediate span of attention (see Lezak, 1995). Also, word-list free recall has been reported to be impaired by one night of total sleep deprivation (Williams, Gieseking, & Lubin, 1966).

Controlled Oral Word Association Test (COWA). The test consisted of three word-naming trials in which subjects were given one minute to generate as many words as they could think of that began with a given letter of the alphabet (e.g. c, f, l), excluding proper nouns, numbers, and the same word with a different suffix. The total number of words generated for the three trials was the score. In addition to the oral production of spoken words, performance on this test is associated with mental flexibility and divergent intelligence (see Lezak, 1995). Horne (1988) has demonstrated that 32-hour sleep deprivation lead to poor performance on a similar test.

Data Analysis

Subjective TST and SE on Friday and Saturday nights were analyzed by a 2 x 2 x 2 (Condition x Day x Sequence) repeated measure ANOVA to test if subjects obtained the same amount and quality of sleep in the two conditions over the weekend and to assess potential sequence effects. One subject was excluded in this analysis because he did not complete the sleep log for the Friday night of placebo condition due to experimenter's mistake. However, his data on

Sunday night and Monday morning, and on DLSMO test were complete and were included for statistical analysis. Measures on Sunday night and Monday morning were analyzed with 2 x 2 (Condition x Sequence) repeated measure ANOVAs to compare the data obtained in the two conditions and to evaluate potential sequence effects. Variables analyzed included: SSS ratings and MVT performance on Sunday evenings, VAMS ratings on Sunday nights and on Monday mornings, sleep log measures and NPSG sleep parameters for Sunday nights, and SSS ratings and cognitive performance on Monday mornings. DLSMO data were analyzed with a 2 x 2 x 2 (Condition x Day x Sequence) repeated measure ANOVA to compare the shift of melatonin onset time from Friday to Monday of the two conditions and to assess the sequence effects.

Results

Subjects' subjective TST on Friday and Saturday nights showed no significant differences between the days (F[1,7] = 0.12, n.s.) and between the conditions (F[1,7] = 0.75, n.s.). The mean TST was 458.4 ± 37.5 minutes for melatonin condition and 455.7 ± 30.3 minutes for placebo conditions. Also, there were no significant Sequence main effect or interactions. Subjects' subjective SE on Friday and Saturday nights were also not significantly different between the days (F[1,7] = .01, n.s.) and between the conditions (F[1,7] = .29, n.s.). The mean SE was 95.1 ± 6.0 % for melatonin condition and 94.1 ± 6.5 %

for placebo conditions. There were no significant Sequence main effect or interactions.

On Sunday evening, subjects rated themselves sleepier on SSS after taking melatonin. Table 1 shows the mean ratings, standard deviations, and ANOVA results for the SSS on Sunday night. The significant differences started 3.5 hours before bedtime, which was 2 hours after melatonin ingestion, and was sustained to the point at one half-hour before bedtime (also see Figure 2). However, the SSS ratings at 1.5 hours and 1 hour before bedtime also showed a significant interaction between Condition and Sequence factors. Subjects rated themselves sleepier the first Sunday night than the second Sunday night both at 1.5 hours (first week mean = 4.3 ± 0.8 vs. second week mean = 3.5 ± 0.7; F[1,8] = 7.1, $p < .05$) and 1 hour (first week mean = 4.9 ± 0.9 vs. second week mean = 4.0 ± 0.9; F[1,8] = 8.1, $p < .05$) before bedtime.

On Sunday evening MVT, none of the variables showed significant difference between the conditions (see Appendix 1). For the MVT at 4.5 hours before bedtime, the numbers of false alarms were 1.0 ± 2.2 for melatonin condition and 0.6 ± 0.8 for placebo condition (F[1,8] = 0.53, n.s.): the numbers of misses were 5.0 ± 7.1 for melatonin condition and 3.6 ± 7.3 for placebo condition (F[1,8] = 0.53, n.s.); the reaction time were 695.5 ± 127.3 msec. for melatonin condition and 726.9 ± 196.4 msec. for placebo condition (F[1,8] = 0.50, n.s.). For the MVT at one hours before bedtime, the numbers of false alarms were 2.4 ± 4.0 for melatonin condition and 1.1 ± 1.5 for placebo condition (F[1,8] = 1.33, n.s.); the numbers of misses were 8.0 ± 12.3 for melatonin condition and 6.4 ± 8.8 for placebo condition (F[1.8] = 0.44, n.s.): the reaction time were 757.9 ± 156.1 msec. for melatonin condition and 730.6 ± 203.5 msec. for placebo condition (F[1,8] = 0.50, n.s.).

On the bedtime VAMS ratings of Sunday night, subjects were shown to be "wearier" (melatonin mean = 72.7 ± 18.6 mm. vs. placebo mean = 47.9 ± 22.7 mm.; F[8.1] = 6.32, $p < .05$) and marginally more "irritable" (melatonin mean = 43.6 ± 33.6 mm. vs. placebo mean = 20.4 ± 22.8 mm.; F[8.1] = 4.85, $p = .06$) on the melatonin condition than on the placebo condition. No other VAMS variables on Sunday night were significantly different between the conditions (see Appendix 2).

As indicated in Table 2, NPSG recording on Sunday night showed shorter SOL (F[1,8] = 5.98, $p < .05$) and shorter latency to stage 2 sleep (F[1,8] = 6.83, $p < .05$) in the melatonin condition than in placebo condition. The average SOL for melatonin condition was 4.0 ± 2.7 min. and for placebo condition was 7.9 ± 4.8 min. The average latency to stage 2 sleep was 6.8 ± 2.1 min. for melatonin condition and 12.3 ± 6.6 for placebo condition. Individual data for SOL and stage 2 onset latency are also presented in Table 3. All the other NPSG variables showed no significant differences between the two conditions. The results from sleep log on Sunday night indicated no significant differences between the two conditions in any of the variables, except for a near significant trend to be less difficult to wake up in the morning in the melatonin condition than in the placebo condition (melatonin mean = 3.0 ± 1.2 vs. placebo mean = 4.3 ± 1.9, F[1,8] = 3.98, *p* = .08; see Appendix 3).

On Monday morning, subjects rated themselves less "sleepy" (melatonin mean = 46.2 ± 33.1 mm. vs. placebo mean = 67.5 ± 18.7 mm., F[1,8] = 6.06, *p* < .05) and "overall feeling better" (melatonin mean = 51.2 ± 14.3 mm. vs. placebo mean = 38.0 ± 10.3 mm., F[1,8] = 9.78, *p* < .05) following the melatonin night than following the placebo night. In addition, ratings of "alert" (melatonin mean = 35.6 ± 21.2 mm. vs. placebo mean = 22.9 ± 13.3 mm., F[1,8] = 4.65, *p* = .06) and "effort to do anything" (melatonin mean = 57.7 ± 21.5 mm. vs. placebo mean = 49.5 ± 20.9 mm., F[1,8] = 4.28, *p* = .07) approached significant (Appendix 4).

SSS ratings on Monday morning showed no significant differences between melatonin and placebo conditions (see Table 1). Also, none of the cognitive tests on Monday morning showed significant differences between the conditions. On the nine-choice simple reaction-time test, subjects' mean reaction time was 620.6 ± 112.9 msec. for the melatonin condition and 637.1 ± 99.8 msec. for the placebo condition (F[1,8] = 1.0, n.s.); mean correct rate was 96.9 ± 2.6 % for the melatonin condition and 97.8 ± 1.6 % for the placebo condition (F[1,8] = 1.1, n.s.). On the COWA, subjects generated an average of 43.4 ± 12.1 words in the melatonin condition and 43.8 ± 11.1 words in the placebo condition (F[1,8] = .03, n.s.). On the WLMT, subjects memorized an average of 9.2 (SD = 3.4) words in the melatonin condition and 9.4 (SD = 3.6) words in the placebo condition (F[1,8] = .05, n.s.). On the MVT, the numbers of false alarms were 0.6 ± 0.8 for melatonin condition and 0.7 ± 1.3 for placebo condition (F[1,8] = 0.09, n.s.); the numbers of misses were 5.6 ± 9.0 for melatonin condition and 2.8 ± 2.8 for placebo condition (F[1,8] = 1.17, n.s.); the reaction time were 655.0 ± 148.1 msec. for melatonin condition and 711.1 ± 232.4 msec. for placebo condition (F[1,8] = 1.98, n.s.; see Appendix 1).

Individual melatonin curves and the DLSMO time on Friday and Monday nights for both conditions were presented in Figure 3 and 4. One subject's (#2) first two samples on Friday night in the placebo condition contained very high levels of melatonin (82.3 and 51.5 pg/ml) and declined rapidly on later samples and yielded a continuous rise later near bedtime. The two samples were considered to be contaminated and were omitted in the figure. The individual data of DLSMO shifts from Friday to Monday for both conditions are also presented in Figure 5.

ANOVA results of DLSMO showed significant interaction between the factors of Condition and Day (F[1,8] = 9.2, p < .05), but no significant Condition (F[1,8] = 4.2, n.s.), Day (F[1,8] = 1.4, n.s.), or Sequence (F[1,8] = .66, n.s.) main effects. Post-hoc comparisons with Newman-Keuls method showed that baseline DLSMOs on Friday nights were not significantly different between the two conditions. However, there was a significant delay of DLSMO from Friday night (2118 h) to Monday night (2149 h) in the placebo condition, but not for the melatonin condition (Friday mean = 2118 h; Monday mean = 2111 h). In reference to their habitual bedtime, the average DLSMO in the placebo condition was 136.8 ± 56.5 min. before habitual bedtime on Friday night and 105.3 ± 83.4 min. before habitual bedtime on Monday night; the average DLSMO in the melatonin condition was 136.5 ± 54.5 min. before habitual bedtime on Friday night and 143.5 ± 73.4 min. before habitual bedtime on Monday night. Table 4 shows the means and standard deviations of melatonin onset times for both Friday and Monday nights in the two conditions.

Although the two baseline DLSMOs measured on Friday night in the two conditions were not different compared by an one-way ANOVA (F[1.9] = 0.001, n.s.) , individual subjects showed variations that ranged from 0.1 to 49.7 minutes (see Figure 3). A Pearson correlation was performed to examine the consistency of the baseline DLSMO measurement and a correlation coefficient of 0.87 was obtained (p = .001). Also, as indicated in Figure 5, individual data showed that the DLSMO was delayed over the weekend in 7 out of the 10 subjects in the placebo condition, ranging from 17.1 to 128.8 min. The other 3 subjects showed minimal to mild advances in DLSMO (1.9, 5.3, and 16.0 min.) In the melatonin condition, 7 subjects demonstrated minimal to moderate advances in DLSMO, ranging from 2.2 to 55.6 min. Although the other 3 subjects showed delays in DLSMO, 2 showed smaller delays in comparison to their DLSMO delays in the placebo condition. Only one subject (#7) showed a greater delay of DLSMO in the melatonin condition than in the placebo condition.

Discussion

The findings of the present study support our hypotheses that a delayed weekend sleep pattern leads to a mild phase delay of the endogenous circadian rhythm and that the phase advance effect of melatonin administration in the late afternoon can counteract the phase shift and alleviate the behavioral consequences of the phase delay.

Previous studies have shown behavioral effects of naturally occurring and simulated delayed weekend sleep pattern (Allen, 1992; Kowalski & Allen, 1995; Lack, 1986; Yang, Spielman, Martinez, Cordero, & Nagata, 1997; also see Experiment 1 of this dissertation). Although the reported sleep and performance problems suggest a delay in endogenous circadian rhythm, no direct evidence of a phase delay in these parameters was demonstrated. In the present study we demonstrated an average delay of 31.6 min. in endogenous melatonin rhythm by measuring the nocturnal onset of endogenous melatonin secretion prior and after two nights of an imposed delayed sleep-wake schedule. This measure provides direct physiological evidence of a phase delay of endogenous circadian rhythms following delayed weekend sleep pattern. However, a potential problem in the current study was the instability of the baseline circadian phase across the two conditions. This may limit the reliability of the estimation of the circadian phase change. Also, it was noted that there was a wide range of individual responses to this delayed sleep pattern. Three of the subjects did not show a delay in their endogenous melatonin rhythm after the delayed weekend, and the DLSMO delays in the rest of the subjects ranged from about a quarter hour to two hours. This suggests that the imposed delayed weekend sleep pattern affected the endogenous rhythm of some individuals but not the others.

In addition, the administration of exogenous melatonin was shown to be an effective treatment of weekend sleep phase delay indicated by an earlier time of DLSMO, a shortened sleep onset latency on Sunday night and improved mood ratings on Monday morning. Although the advance of DLSMO suggested the underlying mechanism to be a phase advance of endogenous circadian rhythm, problems in utilizing melatonin rhythm as the index for the phase advance effect of melatonin administration has been raised (see Czeisler, 1997). Although exogenous melatonin has been consistently shown to advance endogenous melatonin rhythm, it's effect on other indices of circadian rhythmicity have not been consistent. Melatonin administration was shown to shift body temperature and cortisol rhythms in some studies (Deacon & Arendt, 1995; Krauchi, et al., 1995; Sack, et al., 1991) but not in the other studies (Nagtegaal, Kerkhof, Smith, Swart & van der Meer, 1998; Zaidan et al., 1994). It has been suggested that the administration of exogenous melatonin can alter the dynamics of endogenous melatonin due to endocrine feedback effect. Biochemical models have been proposed which suggest that repeated exposure to exogenous melatonin changes the sensitivities of melatonin receptors or the amount of enzymes involved in melatonin synthesis may be responsible for the changes in endogenous melatonin level (Nagtegaal, Kerkhof, et al. 1998). However, this is not likely to be the explanation for our findings since in our study melatonin was administered with only one single dose and the DLSMO post-test was conducted one day after the melatonin administration. Application of other measures to help characterize the endogenous circadian rhythm, such as core body temperature rhythm, may be required to clarify the effect of exogenous melatonin administration in future studies.

Instead of a phase advancing effect, shortening the endogenous period length by exogenous melatonin may be an alternative explanation for our results (see Czeisler, 1997). Since in our study melatonin phase was inferred by measuring the onset time, shortening of *tau* and phase advance are both consistent with an earlier DLSMO time. Employing a continuous measure of circadian rhythmicity for a longer period of time is needed to clarify the role of these two mechanisms.

The sedating effect of melatonin is an alternative explanation for the shortened SOL found in our study. In spite of the short half-life of melatonin, previous studies have shown that the sedating effect of melatonin persists for five hours after administration (Cajochen et al., 1996; Reid, et al., 1996; Tzischinsky & Lavie, 1994). Our results showed that the increase of subjective sleepiness started 2 hours after melatonin administration and lasted up to 5 hours after administration. The administration of melatonin in our study was 5.5 hours before bedtime. Therefore, the sedating property of melatonin may have some residual effect at bedtime, and may have contributed to the decreased SOL.

However, this mild sedating effect cannot explain the beneficial effect on mood Monday morning.

While it is not entirely clear how melatonin affects circadian rhythmicity or how extensively it altered endogenous circadian phase, the behavioral findings in our study suggests melatonin administration can be a beneficial coping strategy for weekend sleep phase delay. A previous survey reported that 17% of college students engage in delayed weekend sleep pattern and are adversely affected (Lack, 1986). While the decrease of SOL on Sunday night after melatonin administration was very consistent across subjects, the average difference was only 3 min. SOL in the placebo condition was short and this limited the improvement possible. The short SOL in placebo condition indicates that the instituted delayed weekend sleep schedule did not produce a clinically significant sleep problem on Sunday night in our sample. Only one subject had a SOL longer than 15 minutes and three had SOL shorter than 5 minutes (see Table 3). This may also explain why cognitive performance on Monday morning showed no significant difference between the two conditions. One possible reason why the phase delay did not generate a greater sleep onset difficulty may be because the subjects were sleep deprived. Subjects had followed the designated sleep schedules with TBT of 7.5 to 8.5 hours in the week prior to the study. The sleep logs data for Saturday night of the placebo condition showed that subjective TST ranged from 7.2 to 8.3 hours (mean = 7.8 hours), and SE ranged from 90.4 to 98.4%. This sleep duration may not be adequate for individuals of this age (Strauch & Meier, 1988)

Another plausible explanation of the failure in producing sleep problem by delaying weekend sleep schedule is that the subjects selected were not from the subgroup of individual who are prone to be affected by a phase delay. Because of the strict requirements for inclusion into the study, such as history of regular sleep-wake schedule, we may have excluded the group of people whose endogenous circadian oscillator is prone to greater delay. Since Evening Type individuals have been shown to have a delayed circadian compared to Morning Type individuals (Bailey & Heitkemper, 1991; Breithaupt & et al., 1978; Clodore, Foret, & Benoit, 1986; Hall, Duffy, Dijk, & Czeisler, 1997), an attempt was made to include only Neither Type and Evening Type people for participation. However, none of the Evening Type potential subjects could follow the controlled sleep-wake schedule and did not complete the study. All of the subjects who finished the study were Neither Type individuals. In order to include Evening Type individuals in future work it may be necessary to allow more flexibility in bedtimes.

In addition to recruitment of Evening Type individuals other groups prone to phase delay should also be investigated. One of these groups is adolescents. Adolescents have been reported to experience a preference for a delayed sleep phase, which suggests a delay in their endogenous circadian rhythm associated with the process of puberty (Carskadon, Vieira & Acebo, 1993; Ishihara, Honma & Miyake, 1990 ;Pelayo, Thorpy & Glovinsky, 1988). In addition, it is very difficult for individuals in this age group to avoid staying up late occasionally during the weekend for social or academic reasons. In addition, their degree of sleep delay during the weekends has been shown to be correlated with poor academic performance (Allen, 1992; Kowalski & Allen, 1995). The administration of melatonin in the late afternoon on Sunday may be a way to preventing the problems associated with a sleep phase delay.

In addition, individuals who have history of DSPS may also benefit from episodic melatonin treatment. After successful treatment of DSPS there is a substantial vulnerability for these individuals to fall back to the delayed sleep pattern if they fail to maintain a regular sleep-wake schedule. The relapse rate of DSPS within 1 year after successful treatment has been reported to be as high as 91.5% (Dagan et al., 1998). Melatonin intake in the late afternoon following the occasions when they need to delay their bedtime can be a practical and useful way to prevent a full fledged relapse to DSPS.

Although a single dose of melatonin may have yielded potential benefits, precaution should be taken because of its sedating effect. Consistent with previous findings (Deacon et al., 1994; Deacon & Arendt, 1995; Tzischinsky & Lavie, 1994), the current study has shown that melatonin increased sleepiness throughout the evening after melatonin intake. General precautions regarding the dangers of operating machinery or driving after melatonin ingestion are advised. Because the sedating as well as the phase shifting effects of melatonin have been shown to be dose dependent (Deacon & Arendt, 1995) the optimal dosage of melatonin which can generate sufficient phase advance while keep the sedating effect to a minimum requires further investigation.

Table 1. Stanford Sleepiness Scale ratings on Sunday evening and Monday morning: Comparison between Melatonin and Placebo conditions (N = 10)

	Melatonin		Placebo			
Time	**Mean**	**SD**	**Mean**	**SD**	**F**	***p***
Sunday Evening						
Bedtime - 4.5hrs	2.2	1.0	1.9	1.0	0.78	.40
Bedtime - 4hrs	2.7	.8	2.4	1.5	0.90	.37
Bedtime - 3.5hrs	4.3	1.3	2.5	1.5	19.64***	.00
Bedtime - 3hrs	3.6	1.0	2.4	1.2	11.52**	.01
Bedtime - 2.5hrs	3.6	1.1	2.7	1.2	32.40***	.00
Bedtime - 2hrs	4.7	1.3	3.4	1.3	12.07**	.01
Bedtime - 1.5hrs[a]	4.5	1.0	3.3	0.8	16.00***	.00
Bedtime - 1hr[a]	5.1	0.9	3.8	1.1	16.90***	.00
Bedtime - 0.5hr	5.6	0.5	4.4	1.0	9.05*	.02
Bedtime	5.8	1.0	4.9	1.4	2.96	.13
Monday Morning						
Wake-up + 1hr	2.4	0.8	2.9	0.7	2.50	.15
Wake-up + 2hrs	1.4	0.5	1.6	0.8	2.67	.14
Wake-up + 3hrs	1.9	1.2	1.8	1.3	0.40	.55

$^{*}p < .05$; $^{**}p < .01$; $^{***}p < .005$

[a] Significant interaction between the factors of Condition and Sequence were also shown in these items.

Table 2. NPSG parameters on Sunday night: Comparison between Melatonin and Placebo condition (N = 10)

	Melatonin		Placebo			
Variable	**Mean**	**SD**	**Mean**	**SD**	**F**	***p***
TST	461.4	25.7	461.3	26.7	0.14	.91
SE	95.6	1.5	95.3	1.5	0.50	.50
TWT%	4.6	1.6	4.8	1.4	0.13	.73
WASO%	3.5	1.6	2.8	1.4	3.04	.12
Stage 1%	6.9	3.3	7.5	4.1	0.49	.50
Stage 2%	57.9	6.6	56.9	5.6	0.31	.59
Stage 3%	9.7	3.9	10.9	2.2	1.38	.27
Stage 4%	3.0	3.9	2.8	2.9	0.03	.86
SWS%	12.7	6.3	13.6	4.3	0.46	.52
NREM%	77.5	4.5	78.1	4.2	0.35	.57
REM%	22.5	4.5	22.0	4.2	0.35	.57
SOL	4.9	2.7	7.9	4.8	5.98*	.04
S2L	6.8	2.1	12.3	6.6	6.83*	.03
SWSL	18.0	4.8	17.6	7.1	0.02	.89
REML	72.6	48.6	71.1	39.4	0.05	.84
# of Arousals	47.6	19.0	50.8	21.0	0.75	.41

TST = total sleep time (min.); SE = sleep efficiency (%); TWT% = percentage of total wake time after light-out; WASO% = percentage of wake time after sleep onset; Stage 1% = percentage of stage 1 sleep; Stage 2 = percentage of stage 2 sleep; Stage 3 = percentage of stage 3 sleep; Stage 4 = percentage of stage 4 sleep; SWS = percentage of slow wave sleep; SOL = sleep onset latency; S2L = stage 2 sleep onset latency; SWSL = SWS onset latency; REML = REM sleep onset latency

*$p < .05$

Table 3. Individual data of designated sleep-wake schedule, sleep onset latency (SOL) and stage 2 onset latency (S2OL) on Sunday night

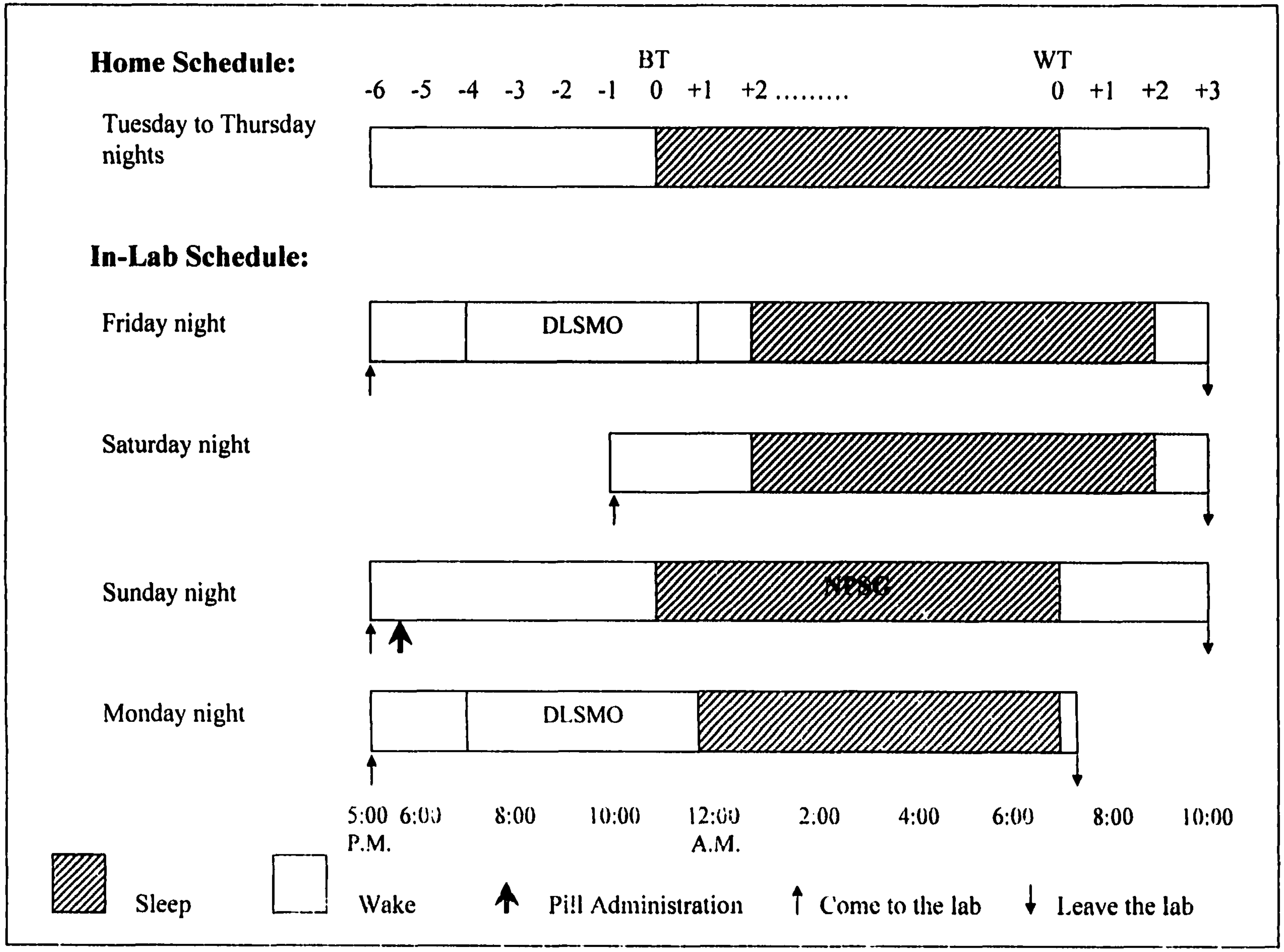
			Schedule		SOL		S2OL	
Subject	Gender	Age	BT	WT	Placebo	Melatonin	Placebo	Melatonin
EM	F	23	00:00	08:30	6.5	3.5	15.2	9.6
WS	M	29	23:00	07:30	11.0	6.0	12.9	6.0
SS	F	21	22:30	06:30	4.0	4.5	4.0	4.5
MM	F	22	23:00	06:30	5.0	3.5	5.0	7.0
CA	F	22	00:30	09:00	9.1	3.5	10.6	7.0
BT	M	21	23:30	07:30	1.5	1.5	12.5	4.0
CK	F	21	00:00	08:00	11.0	3.5	13.5	5.0
BO	F	24	23:30	08:00	7.5	4.0	20.0	6.0
AM	F	19	23:30	07:00	4.9	9.0	4.9	9.0
MP	F	19	23:45	07:15	18.5	10.1	24.1	10.1
Mean		22.1	23:34	07:35	7.9	4.9	12.3	6.8
SD		2.9			4.8	2.7	6.6	2.1

BT = bedtime; WT = wake-up time

Table 4. Time of Dim-Light Salivary Melatonin Onset (DLSMO): Clock time and number of minutes prior to habitual bedtime (BT)

	Friday		Monday		Phase shift (Mon-Fri)	
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Melatonin Condition						
Min. prior to BT	136.5	54.5	143.5	73.4	7.0	35.7
Clock Time	21:18		21:11			
Placebo Condition						
Min. prior to BT	136.8	56.5	105.3	83.4	-31.6	41.3
Clock Time	21:18		21:49			

Figure 1. Experimental procedures for melatonin condition and placebo condition. The procedures for the two conditions were the same except for the pill given. The timings for different experimental activities were decided based on subjects' designated habitual bedtime (BT) and designated habitual wake-up time (WT). The clock time at the button of the figure illustrates the timings of experimental activities for a subject whose designated sleep-wake schedule is 11:00 p.m. to 7:00 a.m.


Home Schedule:
BT
WT
-6 -5 -4 -3 -2 -1 0 +1 +2 ....
0 +1 +2 +3
Tuesday to Thursday nights
In-Lab Schedule:
Friday night
DLSMO
Saturday night
Sunday night
NPSG
Monday night
DLSMO
5:00 P.M.
6:00
8:00
10:00
12:00 A.M.
2:00
4:00
6:00
8:00
10:00
Sleep
Wake
Pill Administration
Come to the lab
Leave the lab

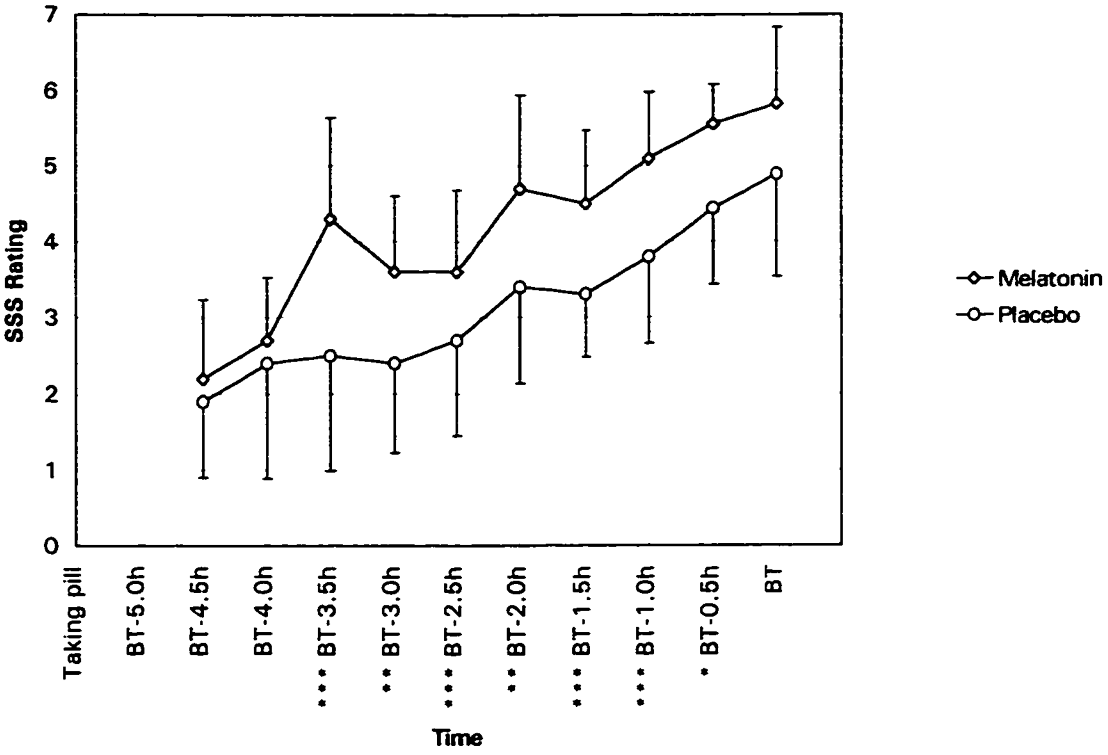


Figure 2. Means of Stanford Sleepiness Scale (SSS) ratings on Sunday night: comparisons between Melatonin and Placebo conditions. Subjects rated their levels of sleepiness every 30 minutes from 4.5 hours before bedtime to bedtime. A pill containing either melatonin or placebo was given at 5.5 hours before bedtime. As indicated in the figure, in the melatonin condition subjects rated themselves significantly more sleepy from 3.5 hours before bedtime (2 hours after taking the pill) to half hour before bedtime compared to the placebo condition.

Figure 3. Pre-test of Dim-light Salivary Melatonin Onset (DLSMO) on Friday Night: (A1) Individual salivary melatonin levels at half hour intervals on the Friday night preceding placebo administration on Sunday night. The doted line represents the melatonin onset criterion at 4 pg/ml. (A2) Individual salivary melatonin levels at half hour intervals on the Friday night preceding melatonin administration on Sunday night. (B1) Individual subjects' melatonin onset time on the Friday night preceding placebo administration on Sunday night. The onset of melatonin secretion was determined by the first interpolated point between salivary melatonin levels below and above 4 pg/ml in which all later samples were above threshold. (B2) Individual melatonin onset time on the Friday night preceding melatonin administration on Sunday night.

Pre-test of DLSMO on Friday Night

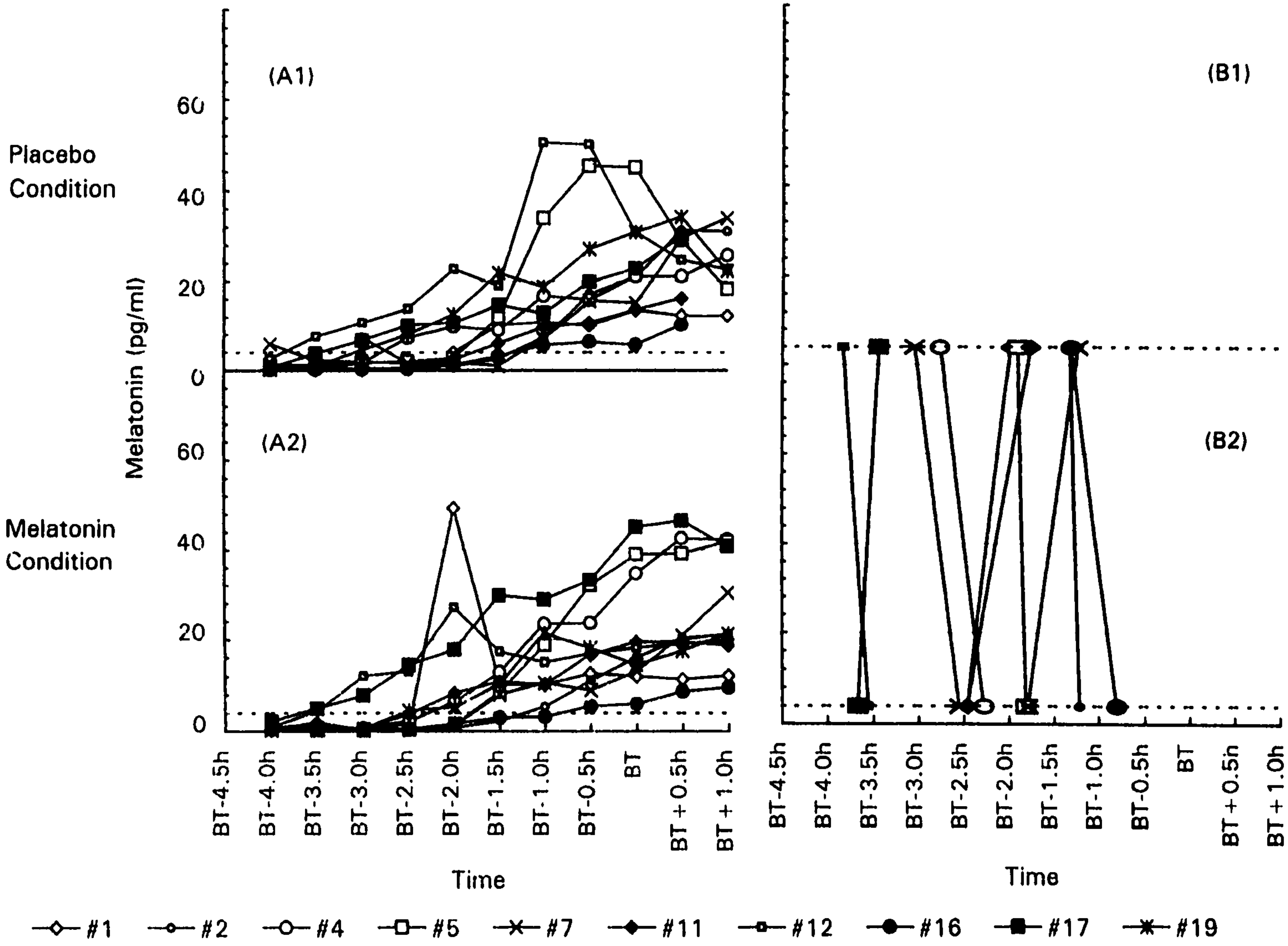


Figure 4. Post-test of Dim-light Salivary Melatonin Onset (DLSMO) on Monday Night: (A1) Individual salivary melatonin level at half hour intervals on the Monday night after placebo administration on Sunday night. The doted line represents the melatonin onset criterion at 4 pg/ml. (A2) Individual salivary melatonin levels at half hour intervals on Monday night after melatonin administration on Sunday night. (B1) Individual melatonin onset time one day after placebo administration on Sunday nigh. The onset of melatonin secretion was determined by the first interpolated point between salivary melatonin levels below and above 4 pg/ml in which all later samples were above threshold. (B2) Individual melatonin onset time one day after melatonin administration on Sunday night.

Post-test of DLSMO on Monday Night

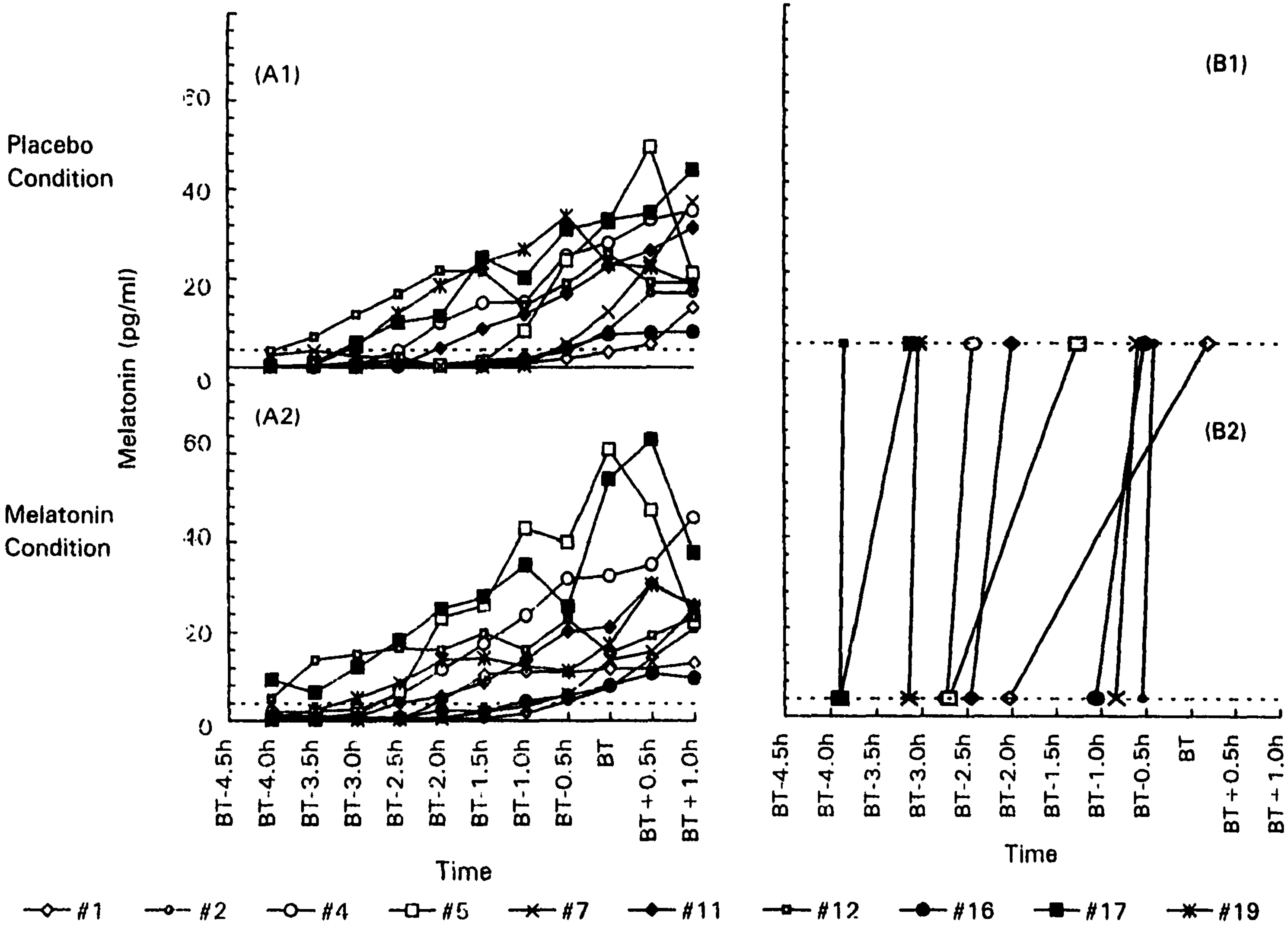
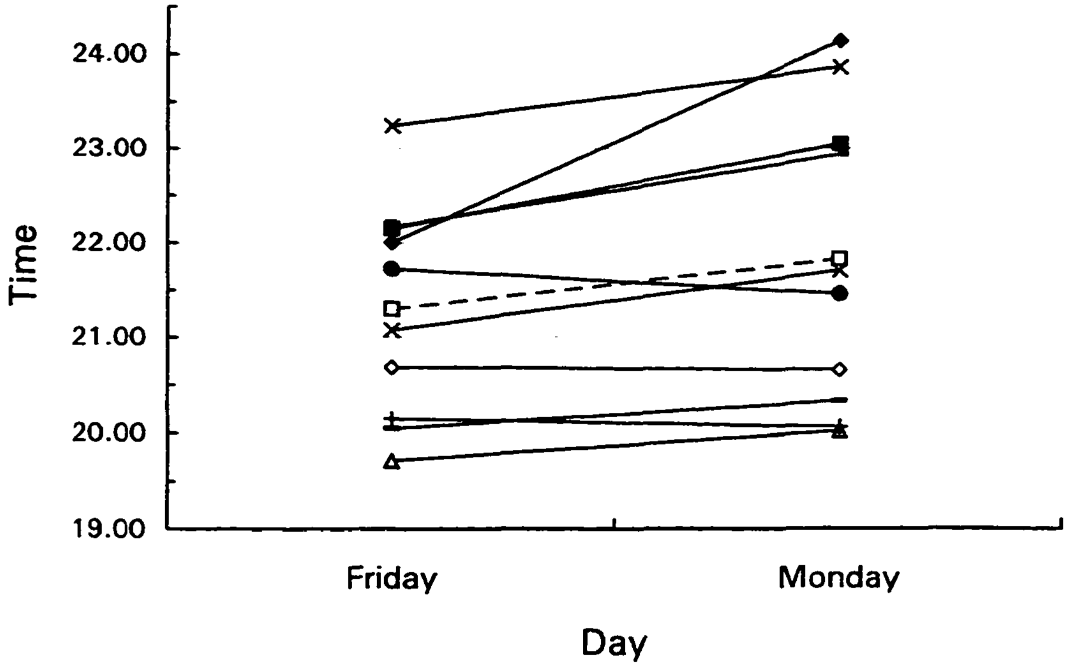
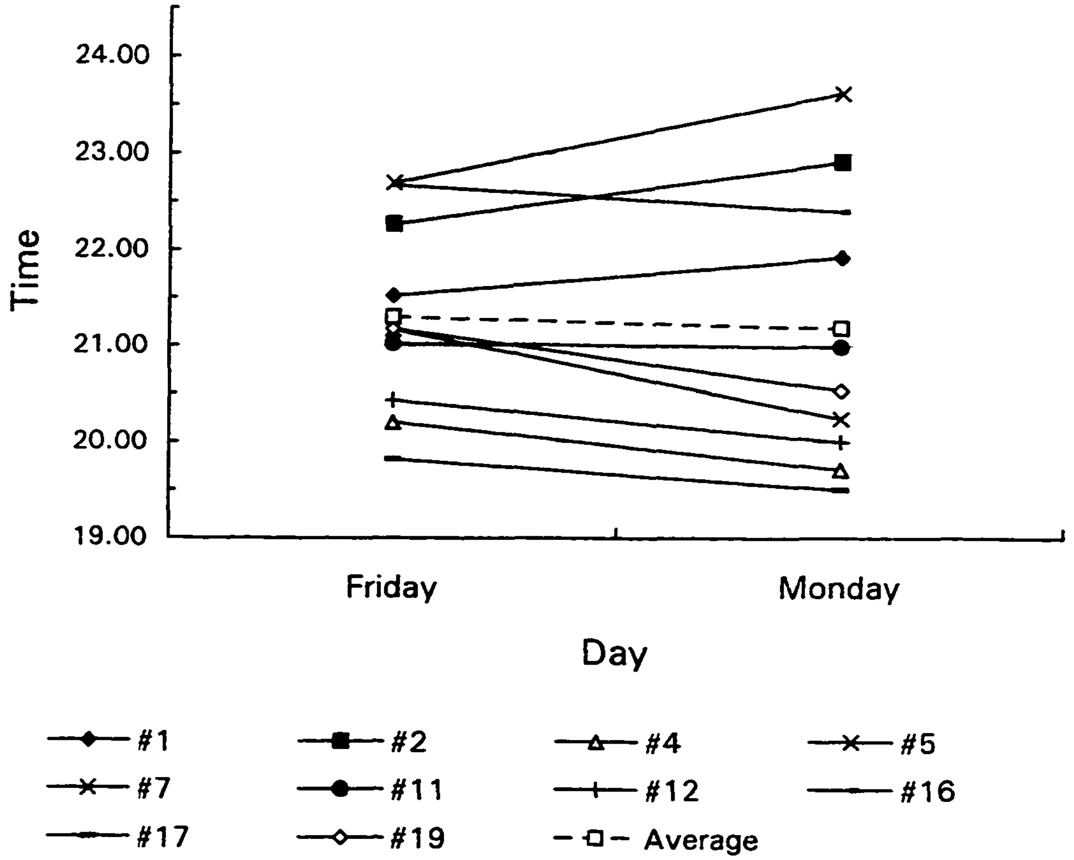


Figure 5. Shifts of Individual Dim-light Salivary Melatonin Onset (DLSMO) Time from Friday to Monday Nights: (A) Shifts of individual melatonin onset time from the Friday before placebo administration on Sunday night to the Monday after placebo administration. The doted line represents the average DLSMO shift. (B2) Shifts of individual melatonin onset time from the Friday before melatonin administration on Sunday night to the Monday after melatonin administration. The doted line represents the average DLSMO shift.

(A) Placebo Condition



(B) Melatonin Condition



Appendix 1. Table for Multiple Vigilance Test (MVT) variables on Sunday evening and Monday morning: Comparison between Melatonin and Placebo conditions (N = 10).

	Melatonin		**Placebo**			
Variable	**Mean**	**SD**	**Mean**	**SD**	**F**	***p***
Sunday Evening (4.5 hrs before bedtime)						
False Alarm	1.0	2.2	0.6	0.8	0.53	.49
Miss	5.0	7.1	3.6	7.3	0.20	.67
Reaction Time	695.5	127.3	726.9	196.4	0.50	.50
Sunday Evening (1 hrs before bedtime)						
False Alarm	2.4	4.0	1.1	1.5	1.33	.28
Miss	8.0	12.3	6.4	8.8	0.44	.53
Reaction Time	757.9	156.1	730.6	203.5	0.50	.50
Monday Morning						
Hit	54.4	9.0	57.2	2.8	1.17	.31
Miss	5.6	9.0	2.8	2.8	1.17	.31
Reaction Time	655.0	148.1	711.1	232.4	1.98	.20

Appendix 2. Table for Visual Analog Mood Scale (VAMS) ratings on Sunday night: Comparison between Melatonin and Placebo conditions (N = 10).

	Melatonin		**Placebo**			
Item	**Mean**	**SD**	**Mean**	**SD**	**F**	***p***
Alert	23.1	19.8	36.0	29.2	2.33	.17
Sad	14.9	18.4	17.6	22.3	0.10	.76
Tense	30.7	25.3	32.9	22.5	0.26	.62
Effort	72.1	20.1	56.9	22.3	1.92	.20
Happy	46.1	23.6	46.6	23.1	0.01	.93
Hungry	19.5	23.1	36.1	36.8	1.50	.26
Weary	72.7	18.6	47.9	22.7	6.32*	.04
Irritable	43.6	33.7	20.4	22.8	4.85	.06
Sleepy	81.8	17.7	70.9	26.5	0.90	.37
Angry	16.7	18.6	16.3	26.8	0.00	.97
Sexual	20.7	21.0	22.5	25.6	0.04	.86
Overall	46.6	18.7	52.8	20.5	1.28	.29

*$p < .05$

Appendix 3. Table for Subjective sleep parameters on Sunday night measured by sleep log: Comparison between Melatonin and Placebo conditions (N = 10).

	Melatonin		Placebo			
Variable	Mean	SD	Mean	SD	F	*p*
Alert	5.7	0.8	5.6	0.5	0.12	.74
Fatigue	2.3	1.0	3.0	1.3	1.63	.24
SOL	11.0	8.7	11.3	4.4	0.03	.86
WASO	8.1	12.4	5.9	5.9	0.32	.59
Sleep Quality	5.3	1.4	4.7	1.3	1.71	.23
DW	3.0	1.2	4.3	1.9	3.98	.08

Alert = overall level of alertness on Sunday; Fatigue = overall level of fatigue on Sunday; SOL = sleep onset latency (min.); WASO = wake time after sleep onset (min.); SQ = subjective rating of sleep quality; DW = subjective rating of difficulty to wake up on Monday morning

$^{*}p < .05$; $^{**}p < .01$; $^{***}p < .005$

Appendix 4. Table for Visual Analog Mood Scale (VAMS) ratings on Monday morning: Comparison between Melatonin and Placebo conditions (N = 10).

	Melatonin		Placebo			
Item	**Mean**	**SD**	**Mean**	**SD**	**F**	***p***
Alert	35.6	21.3	22.9	13.3	4.65	.06
Sad	15.9	21.5	5.0	3.7	3.38	.10
Tense	23.8	26.9	18.3	11.6	0.37	.56
Effort	57.7	21.6	49.5	20.9	4.28	.07
Happy	37.6	15.5	35.0	18.2	0.38	.55
Hungry	37.9	25.9	34.0	35.2	0.13	.73
Weary	15.4	28.1	51.9	19.9	2.15	.18
Irritable	26.2	32.4	27.2	26.1	0.02	.88
Sleepy	46.2	33.1	67.5	18.7	6.06*	.04
Angry	17.1	23.7	6.4	6.1	3.00	.12
Sexual	16.6	18.1	13.0	16.2	3.36	.10
Overall	51.2	14.3	38.0	10.3	9.78*	.01

*$p < .05$

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IMAGE EVALUATION
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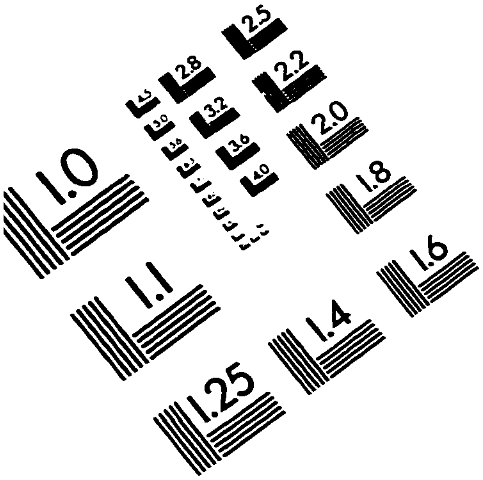

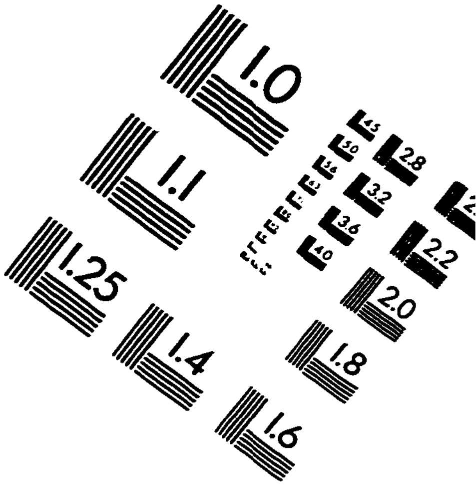

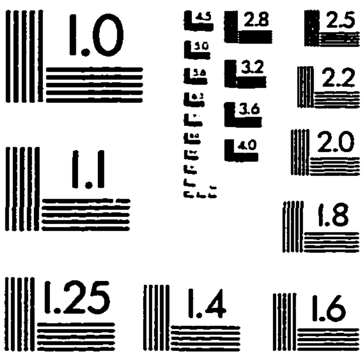

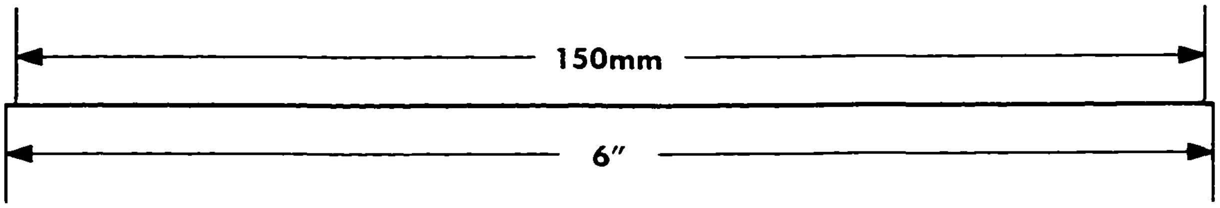

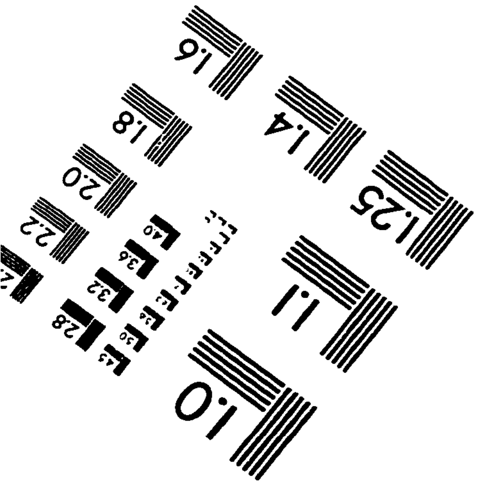

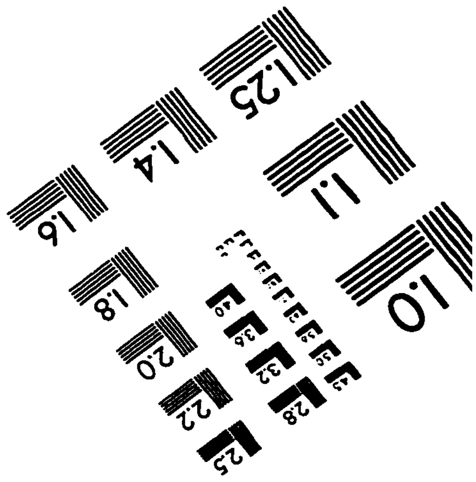

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